

**SYNTHETIC STUDIES ON THE  
AZINOTHRICIN FAMILY OF ANTITUMOUR  
ANTIBIOTICS**

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A thesis presented to the University of London in  
partial fulfilment of the requirements of the degree  
of Doctor of Philosophy

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## **ACKNOWLEDGEMENTS**

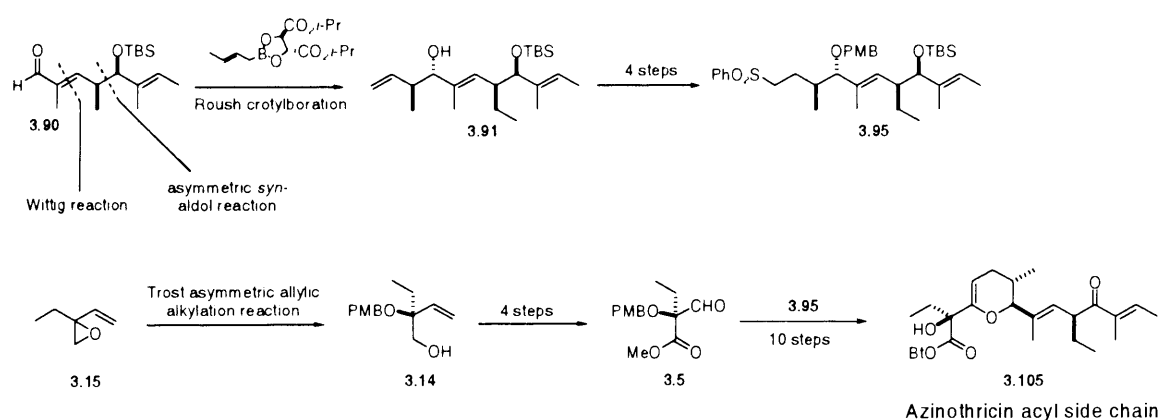
Firstly, I would like to thank Professor Karl Hale for his guidance and support throughout my PhD studies. His generosity with his time and his infectious enthusiasm for chemistry will not be forgotten. I am also very grateful to Soraya for her tuition in practical organic chemistry and her efficient organisation of the Hale laboratory.

During my time in the Hale group I have had the privilege of working with many excellent colleagues. In particular, I would like to thank Linos and Shahid for their help in the early part of my PhD studies, and Marcus for providing great comradeship and banter for over three years. I am very grateful Paschalis for his advice and friendship, and Samuel for providing a bit of light relief. I also thank the French contingent – Matthias, Amandine and Guillaume – and the newer group members – Yi, Russell and Mehrnoosh – for all their assistance and good companionship.

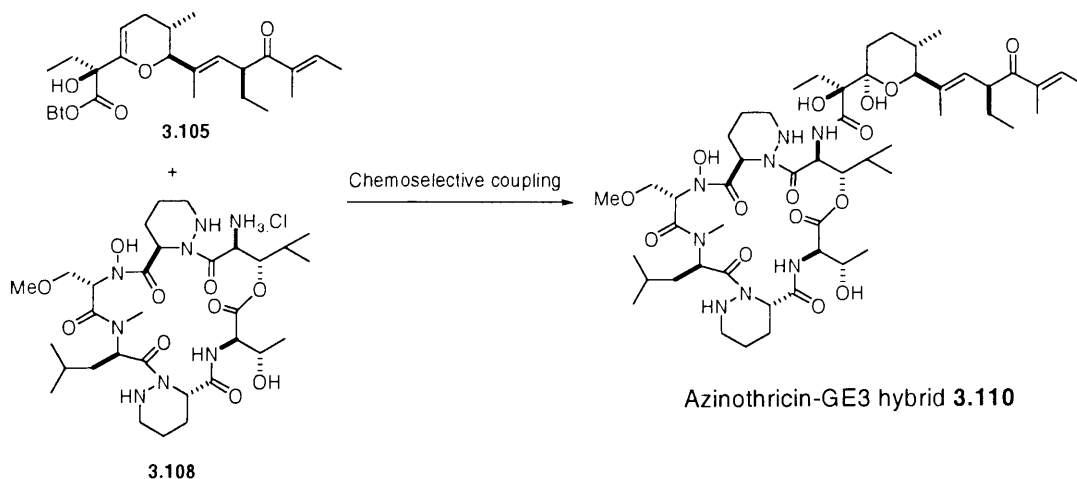
Finally, I thank my mother for her invaluable support throughout my academic studies.

## ABSTRACT

A first synthesis of the acyl side chain of azinotrichin and a second-generation route to the A83586C side chain is described in this thesis. The successful strategy was based on an asymmetric aldol reaction, a stereoselective Roush-type crotylboration and a Trost asymmetric allylic alkylation reaction to set the stereocentres of the key intermediates **3.95** and **3.5**, which were subsequently coupled together to give the side chain fragment **3.105** after 10 further steps.



The total synthesis of several A83586C/azinotrichin analogues is also described. These hybrid structures have been formed via a chemoselective coupling between the *N*-hydroxybenzotriazole activated ester of the acyl side chain and the appropriate fully deprotected cyclodepsipeptide hydrochloride salt. The first total syntheses of the natural products azinotrichin and kettapeptin have also been achieved by this strategy.





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**List of common abbreviations used in the text**

AAA	asymmetric allylic alkylation
AD	asymmetric dihydroxylation
AIBN	2,2'-azobisisobutyronitrile
Alloc	allyloxycarbonyl
APC	anaphase-promoting complex
9-BBN	9-borabicyclo[3.3.1]nonane
Bn	benzyl
BOP-Cl	bis(2-oxo-3-oxazolidinyl)phosphinic chloride
BOP reagent	(benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate
CDK	cyclin-dependent kinase
CDKI	cyclin-dependent kinase inhibitor
Cp	cyclopentadienyl
dba	<i>trans, trans</i> -dibenzylidene acetone
DCC	1,3-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DET	diethyl tartrate
DIBAL-H	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMF	<i>N,N</i> -dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1 <i>H</i> )-pyrimidinone
DMSO	dimethyl sulfoxide
d. r.	diastereomeric ratio
ee	enantiomeric excess
Fmoc	9-fluorenylmethoxycarbonyl
HATU	<i>O</i> -(7-azabenzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium hexafluorophosphate
HMPA	hexamethylphosphoramide

HOBt	1-hydroxybenzotriazole
IC <sub>50</sub>	concentration of a drug that is required for 50% of maximum inhibition <i>in vitro</i>
Im	imidazole
LDA	lithium diisopropylamide
MS	molecular sieves
Ms	methanesulfonyl
NaHMDS	sodium bis(trimethylsilyl)amide
NBS	<i>N</i> -bromosuccinimide
PDC	pyridinium dichromate
PMB	4-methoxybenzyl
PMP	4-methoxyphenyl
PPTS	pyridinium 4-toluenesulfonate
pRb	retinoblastoma protein
pyr	pyridine
Red-Al	sodium bis(2-methoxyethoxy)aluminium hydride
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBHP	<i>tert</i> -butyl hydroperoxide
TBS	<i>tert</i> -butyldimethylsilyl
TCF	T-cell factor
Teoc	2-(trimethylsilyl)ethoxycarbonyl
TES	triethylsilyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TPAP	tetra- <i>n</i> -propylammonium perruthenate
Troc	2,2,2-trichloroethoxycarbonyl
Ts	4-toluenesulfonyl
Z	benzyloxycarbonyl

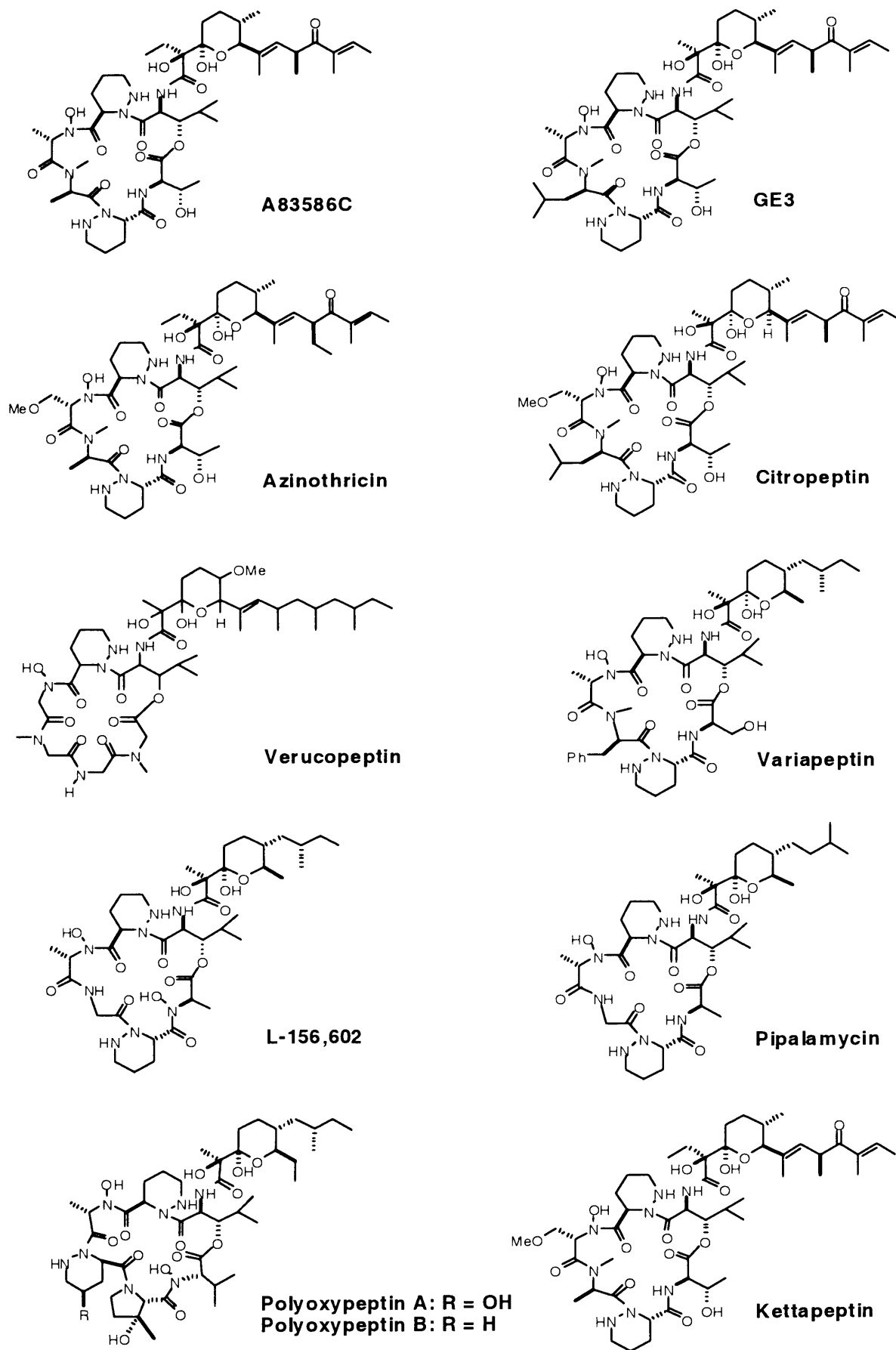
## Chapter 1 Introduction

### 1.1 The azinothricin family of antitumour antibiotics

The azinothricin-type antitumour antibiotics constitute a family of cyclodepsipeptide polyketide natural products that were first encountered in the late 1980s. The members of this group, which will be discussed individually later in this section, all possess a complex 19-membered cyclodepsipeptide core (i.e. a cyclic peptide containing at least one ester linkage<sup>1</sup>) that is linked via an amide bond to an ornate polyketide tetrahydropyranyl side chain. This structural complexity renders these molecules highly attractive targets for synthetic organic chemists, as successful approaches to members of this family will be likely to develop new synthetic methodology and strategies, as well as refine existing reaction technology.

However, the main attraction of azinothricin-type natural products as targets for synthesis is their potent biological activity, with members of the family exhibiting a wide range of antitumour and antimicrobial effects. As such, several of these molecules possess potential therapeutic value. Also, they could serve as useful probe molecules for investigating the regulatory pathways that control cell functioning. In particular, the family member A83586C functions as a powerful inhibitor of E2F transcription factor activity within cancer cells via a range of mechanisms, as discussed in Section 1.2. A83586C also inhibits transactivation from the TCF4 promoter ( $IC_{50} = 3$  nM) in HCT-116 colon cancer cells and, as a consequence, inhibits Wnt signaling.<sup>2</sup> If the mechanisms behind these processes could be discovered, it might be possible to develop small molecule dual-action E2F/TCF4 transcription factor inhibitors with a superior pharmacological profile to A83586C.

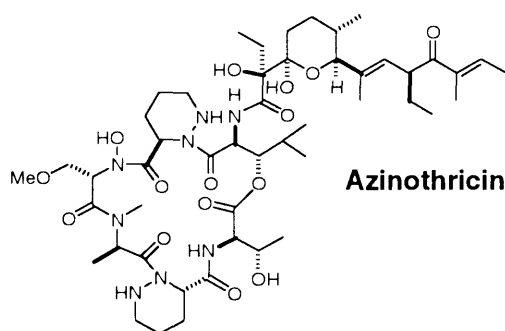
A further incentive for developing synthetic routes to the azinothricin family is the possibility of analogue construction. Indeed, the bipartite nature of these structures suggests the formation of hybrid molecules, with the cyclodepsipeptide of one family member joined to the acyl side chain of another. In this way, a molecule that is more biologically potent and/or easier to manufacture may be discovered.



Scheme 1.1 The A83586C family of antitumour antibiotics

Each member of the azinothricin family (Scheme 1.1) contains a conserved tripeptide motif of (2*S*, 3*S*)-3-hydroxyleucine, (3*R*)-piperazic acid and an *N*-hydroxy-amino acid as part of its cyclodepsipeptide core. The tetrahydropyranyl side chain is always linked to the ring via the hydroxyleucine nitrogen. Azinothricin, A83586C, citropeptin, GE3 and kettapeptin possess very similar structures, and the discovery, isolation and biological activities of these compounds, which have been of most interest to the Hale group, will be considered together. Verucopeptin has a markedly different cyclodepsipeptide core and side chain, both with unknown stereochemistry. Variapeptin, L-156,602 and pipalamycin are composed of nearly identical cyclodepsipeptide rings and tetrahydropyranyl side chains of slightly reduced stereochemical complexity compared to azinothricin. Polyoxypeptins A and B have a similar acyl side chain to variapeptin and L-156,602, but a distinctive cyclodepsipeptide structure.

#### Azinothricin, A83586C, citropeptin, GE3 and kettapeptin



##### Roche Data on Azinothricin

MIC values from <0.008 to 0.063  $\mu\text{g/mL}$   
Vs a range of Gram-positive bacteria  
Antitumour activity not so far evaluated.

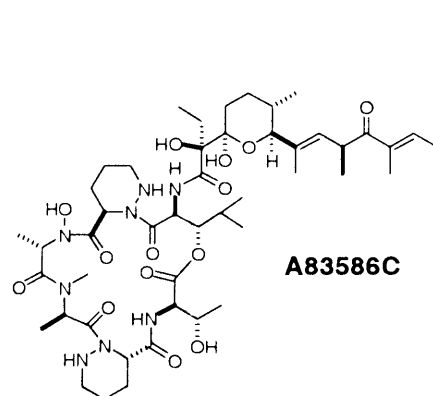
##### Toxicity Profile

LD<sub>50</sub> in mice = 10 mg/kg intravenously  
LD<sub>50</sub> in mice = 420 mg/kg sub-cutaneously  
LD<sub>50</sub> in mice = >500 mg/kg orally

#### Scheme 1.2 Pharmacological properties of azinothricin

Azinothricin, the prototype of this class of natural products, was isolated from the culture filtrate of *Streptomyces sp. X-14950* by Maehr<sup>3</sup> and colleagues at Hoffman-La Roche in 1986 during their search for new compounds with powerful antibiotic effects. The culture filtrate showed active *in vitro* activity against Gram-positive bacteria, and the active component was isolated in crystalline form and characterised as azinothricin by X-ray studies. In terms of potency, its MIC values ranged from <0.008 to 0.016  $\mu\text{g/ml}$  for 31 strains of *Staphylococcus aureus*; 0.063  $\mu\text{g/ml}$  for 16 strains of *Enterococcus faecalis*; 0.016  $\mu\text{g/ml}$  for 2 strains of *Streptococcus pyogenes*; and <0.008  $\mu\text{g/ml}$  for 2 strains of *Streptococcus pneumoniae*.

Azinothricin was also active against the two anaerobes *Clostridium histolyticum* and *Clostridium septicum* with MIC values of 0.001  $\mu\text{g/ml}$ , but was much less effective against Gram-negative bacteria and fungi. However, azinothricin was shown to be highly toxic to mice, curtailing any possibility of its clinical development as an antibacterial drug.



#### Eli Lilly Data on A83586C

$\text{IC}_{50} = 0.0135 \mu\text{g/mL}$  Vs CCRF-CEM Human T-Cell  
Leukaemia Cells

#### NOVARTIS/UCL Data on A83586C

$\text{IC}_{50} = 40 \pm 10 \text{ nM}$  Vs HCT-116 Human Colon Cancer Cells  
 $\text{IC}_{50} = 60 \pm 30 \text{ nM}$  HT-29 Cancer Cells  
 $\text{IC}_{50} = 90 \pm 10 \text{ nM}$  MDA-MB-435 Cancer Cells  
 $\text{IC}_{50} = 90 \pm 30 \text{ nM}$  MCF-7 Human Breast Cancer Cells  
 $\text{IC}_{50} = 30 \pm 10 \text{ nM}$  A549 Human Lung Cancer Cells  
 $\text{IC}_{50} = 160 \pm 30 \text{ nM}$  PC-3M Human Prostate Cancer Cells  
 $\text{IC}_{50} = 80 \pm 10 \text{ nM}$  U2OS Human Uterine Cancer Cells

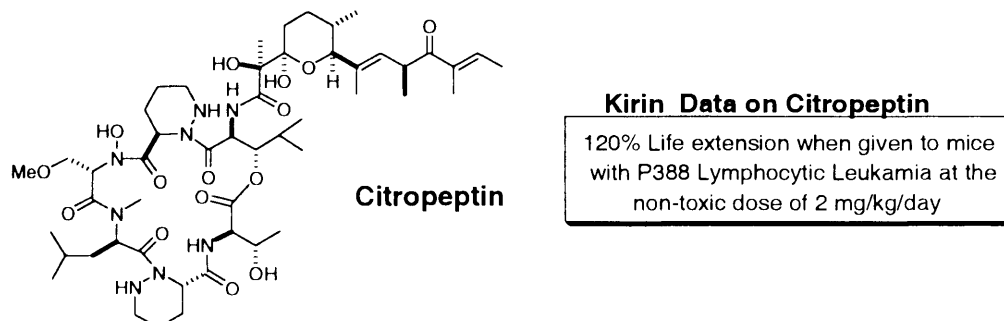
Induces cell-cycle arrest and pRb hypophosphorylation, reduces E2F1 protein, cyclin A protein, and cyclin D protein (by Western blotting). Does not disrupt E2F/DP/DNA binding.

### Scheme 1.3 Pharmacological properties of A83586C

The next member of the group to be discovered was A83586C. This molecule was isolated from fermentation broths of the Guam soil micro-organism *Streptomyces karnatakensis* by Smitka<sup>4</sup> and co-workers at Eli Lilly in 1988. A83586C possesses a very similar molecular structure to azinothricin; the only differences are that the A83586C cyclodepsipeptide has an *N*-hydroxyalanine amino acid unit substituted for the *N*-hydroxy-*O*-methyl-L-serine unit of azinothricin, and the A83586C pyran side chain has a methyl group at the C-37 stereocentre, as opposed to an ethyl group in azinothricin. A83586C also closely resembles azinothricin in terms of biological activity; it demonstrates the same Gram-positive activity *in vitro*, as well as the same toxicity *in vivo*.

However, unlike azinothricin, A83586C has been found to be a remarkably effective antitumour agent. It shows activity against a broad range of human tumour cell lines, exhibiting  $\text{IC}_{50}$ s of 13-160 nM versus all eight of the cell lines (including MCF-7 human breast cancer cells and A549 human lung cancer cells) against which it was screened (Scheme 1.3).

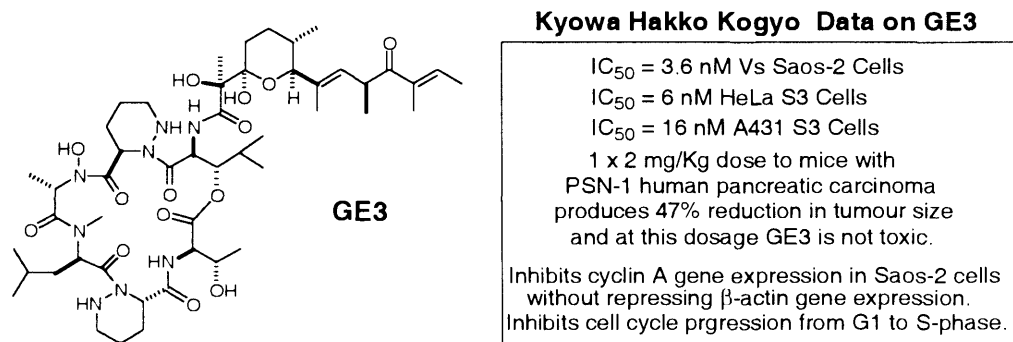
The mechanism of this anticancer activity has been shown to involve inhibition of the Wnt/APC/ $\beta$ -Catenin/TCF-4 cell signalling pathway (see Section 1.2).



**Scheme 1.4** Pharmacological properties of citropeptin

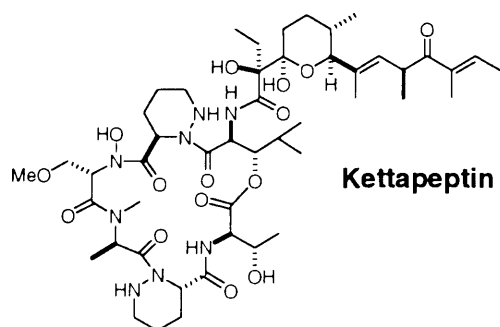
The third of these molecules to be isolated was citropeptin, discovered in 1990 by Nakagawa<sup>5</sup> at the Kirin Brewery Company in Japan (Scheme 1.5). It was extracted from culture K3619, a strain of *Streptomyces flavidovirens*, obtained from a soil sample collected in Brazil. The structure of citropeptin was determined by comparative NMR studies with azinothricin and A83586C. The only points of diversity of citropeptin from azinothricin are: (i) the *N*-methyl-D-leucine amino acid instead of the *N*-methyl-D-alanine, (ii) a methyl group at the quaternary C-28 stereocentre in place of an ethyl group, and (iii) a methyl group at C-37 in place of an ethyl group. Citropeptin is a strong antibiotic that also displays potent cytotoxicity against murine P388 leukaemia cells ( $IC_{50} = 0.02 \mu\text{g/ml}$ ) and B16 melanoma cells ( $IC_{50} = 0.01 \mu\text{g/ml}$ ). Crucially, it confers a 120% life extension on mice bearing P388 lymphocytic leukaemia when administered at doses of 2 mg/kg/day (Scheme 1.4). This key discovery reawakened synthetic interest in this class of molecule.





### Scheme 1.5 Pharmacological properties of GE3

GE3 was isolated from culture broths of *Streptomyces sp. GE3*, a microorganism present in a soil sample taken from the Shimane prefecture, Japan. This discovery took place in 1997 by Sakai<sup>6,7</sup> and his co-workers at Kyowa Hakko Kogyo Co. Ltd. Again the structure of the newly discovered natural product was shown to be very similar to the known A83586C-type molecules. In fact, GE3 had exactly the same pyran side chain as citropeptin. Its cyclodepsipeptide was also very similar to that of citropeptin; identical except for the substitution of *N*-hydroxy-D-alanine (GE3) for the *N*-hydroxy-*O*-methyl-L-serine (citrapeptin). GE3 also shares some of citropeptin's biological activity; it displays potent cytotoxicity against various human and mouse cell lines with IC<sub>50</sub> values ranging from 6 nM to 16 nM. The *in vivo* antitumour effect of GE3 against a human tumour was examined in a human xenograft mouse tumour model. A single dose of GE3 at 2 mg/kg was shown to cause a 47% reduction in tumour size in mice transplanted with PSN-1 human cancer carcinoma after 11 days. Importantly, GE3 did not pose any serious toxicity problems at this dosage. The mechanism of the antitumour activity of GE3 was suggested to involve inhibition of the E2F transcription factor (see Section 1.3).



#### Gottingen Data on Kettapeptin

MIC value of 3.75  $\mu\text{g/mL}$  vs *Bacillus subtilis*.  
 Strong antibacterial activity against  
*Streptomyces viridochromogenes*,  
*Staphylococcus aureus* and *Escherichia coli*,  
 determined semi-quantitatively.  
 Highly active against human lung cancer,  
 breast tumour, melanoma, kidney tumour  
 and uterus tumour cell lines with  $\text{IC}_{50}$  values  
 of  $<0.6 \mu\text{g/ml}$ .

#### Scheme 1.6 Pharmacological properties of kettapeptin

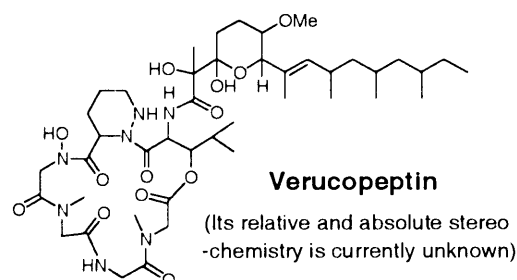
More recently, kettapeptin was isolated from the ethyl acetate extract of the strain *Streptomyces* sp. isolate GW99/1572 by the Laatsch research group at the University of Gottingen (Scheme 1.6).<sup>8</sup> The structure of this new hexadepsipeptide antibiotic was determined by various 1D and 2D NMR techniques, mass spectrometry and by comparison of the NMR data with those of azinothricin and A83586C. The structure and absolute configuration of kettapeptin were confirmed by crystal structure analysis, which showed that this new molecule was composed of an A83586C-type acyl side chain linked to the azinothricin cyclodepsipeptide core.

Kettapeptin was shown to exhibit growth inhibitory activity against *Bacillus subtilis* (with a MIC value of 3.75  $\mu\text{g/ml}$ ), *Streptomyces viridochromogenes*, *Staphylococcus aureus* and *Escherichia coli*. In addition, kettapeptin was found to be highly active at inhibiting the growth of human cancer cell lines LXFA 629L and LXFL 529L (lung cancer), MAXF 401NL (breast tumour), MEXF 462NL (melanoma), RXF 944L (kidney tumour) and UXF 1138L (uterus tumour) with  $\text{IC}_{70}$  value of  $<0.6 \mu\text{g/ml}$ .

When one considers azinothricin, A83586C, citropeptin, GE3 and kettapeptin as a group, perhaps their most striking property is the sheer range of biological activity exhibited by such similar structures. For example, while A83586 exhibits strong antibacterial activity, its close relative GE3 (which differs from A83586C at just two sites) shows only very weak antibiotic effects. The anticancer profiles of the compounds are also highly divergent. This obviously suggests that designed analogues or hybrids of this class of natural products could have the

potential to be even more biologically active, perhaps giving rise to highly effective and selective antitumour agents.

### Verucopeptin



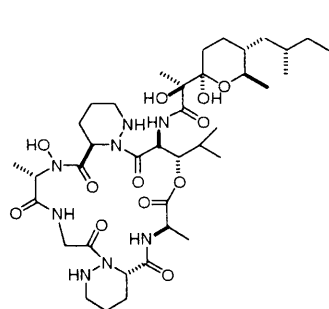
#### Bristol-Myers Squibb Data on Verucopeptin

$IC_{50} = 0.004 \mu\text{g/mL}$  Vs B16-F10 Melanoma Cells  
 $IC_{50} = 0.08 \mu\text{g/mL}$  Vs P388 Leukaemia Cells  
 $IC_{50} = 0.04 \mu\text{g/mL}$  Vs HCT-116 Human Colon Cancer Cells  
 T/C = 146% at 0.5 mg/kg/day Vs B16 Melanoma in Mice  
 (at same dosage mitomycin C showed T/C = 138%)  
 T/C = 162% at 2 mg/kg/day Vs B16 Melanoma in Mice

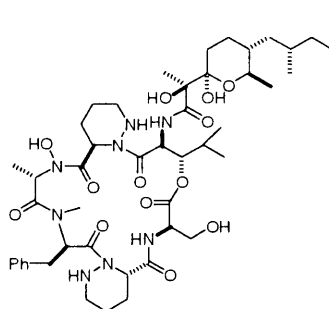
### Scheme 1.7 Pharmacological properties of verucopeptin

Verucopeptin is both a powerful antibiotic and antitumour agent (Scheme 1.7). It was isolated from the fermentation broths of *Actinomadura verrucospora* Q886-2, a microorganism discovered in a Philippine soil sample.<sup>9,10,11</sup> Research into the properties of this molecule has been carried out at the Bristol-Myers Squibb research institute in Tokyo. Verucopeptin was found to significantly extend the life expectancy of mice with B16 melanoma, giving rise to a 162% life extension when given at the low dosage of 2 mg/kg/day. After detailed spectral analysis, verucopeptin was shown to be a member of the azinothricin family, although its relative and absolute stereochemistry remains unknown.

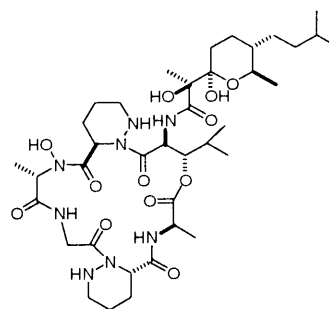
### L-156,602, Variapeptin and Pipalamycin



**L-156,602**



**Variapeptin**



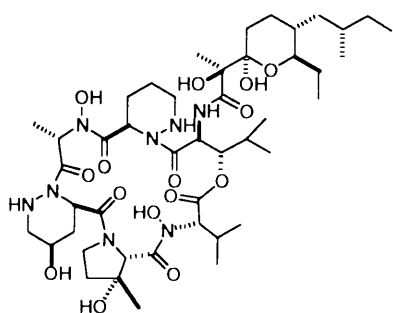
**Pipalamycin**

Besides the very closely related structures of azinothricin, A83586C, citropeptin and GE3, the azinothricin family includes several other natural products of slightly more diverse molecular structure. L-156,602 was isolated in 1990 from cultures of *Streptomyces* sp. MA6348 by Hensens<sup>12</sup> and co-workers at Merck Sharp Dohme, and was synthesized in an optically pure form later that year by Caldwell and Durette<sup>13,14</sup> at the same company. It was found to be an inhibitor of anaphylatoxin C5a, binding to its receptor on human neutrophils. C5a antagonists are of interest on account of their significant therapeutic potential for the treatment of inflammatory disorders and allergic disease states.

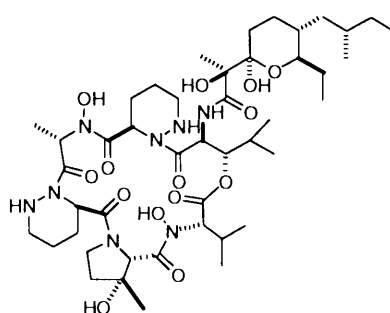
The antibiotic variapeptin, nearly identical in structure to L-156,602, was isolated by Nakagawa<sup>15</sup> and co-workers at the Kirin Brewery Company in 1990. It was extracted from culture K2919, a strain of *Streptomyces variabilis* taken from a soil sample collected in Bosque, Brazil. Variapeptin exhibits very potent activity against Gram positive bacteria *in vitro*, and demonstrates strong cytotoxicity against P388 leukaemia cells ( $IC_{50} = 0.01 \mu\text{g/ml}$ ). However, it was found to be toxic to mice when administered at 5 mg/kg, and it was inactive *in vivo* against P388 lymphocytic leukaemia at the highest non-toxic dose.

Pipalamycin<sup>16</sup> was recently isolated from a culture filtrate of *Streptomyces* sp. ML297-90F8. This compound was found to induce cell death in apoptosis-resistant human pancreatic adenocarcinoma AsPC-1 cells at  $0.3 \mu\text{g/ml}$  in 24-48 hours. These cell deaths were confirmed to be apoptosis by induction of nuclear fragmentation. Pipalamycin also displayed antibacterial activity against Gram-positive bacteria such as *Staphylococcus aureus* and *Micrococcus luteus*.

## Polyoxypeptins A and B



**Polyoxypeptin A**



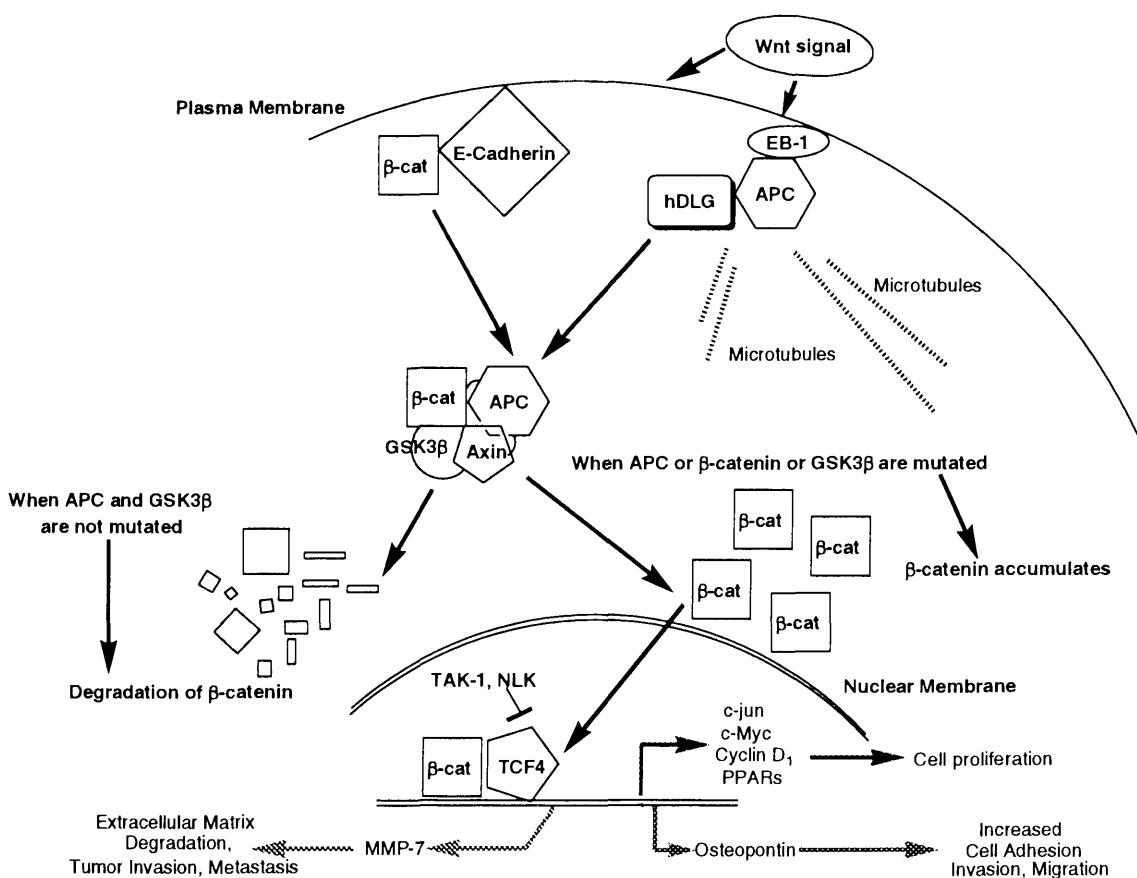
**Polyoxypeptin B**

Polyoxypeptins A and B were isolated from the culture broth of *Streptomyces* sp. in 1998 by Umezawa and co-workers.<sup>17,18,19</sup> Polyoxypeptin A has attracted great interest because it strongly induces apoptosis in drug resistant human pancreatic carcinoma with an  $IC_{50}$  of 80 ng/mL after 24 h. The structure of polyoxypeptin was unambiguously established by X-ray crystallographic analysis and degradation studies.

### 1.2 The Wnt-1/APC/ $\beta$ -catenin/TCF-4 signalling pathway

A stepwise model for colorectal tumourigenesis was proposed by Fearon and Vogelstein<sup>20</sup> in 1990, and subsequently verified by several other research groups. It involves four specific gene mutations. Several of the signalling pathways responding to these mutations have now been discovered, including the APC/ $\beta$ -catenin pathway (Scheme 1.8).  $\beta$ -Catenin is a multifunctional intracellular protein involved in cell-cell adhesion and Wnt-signalling during development. Most of the cellular  $\beta$ -catenin is situated at the cell membrane between cell-cell junctions, where it mediates cadherin-based cell adhesion through interactions with the cytoplasmic regions of E-cadherin and  $\alpha$ -catenin. Under normal circumstances, the concentration of  $\beta$ -catenin in the cytoplasm and nucleus is usually very low. Accumulation of  $\beta$ -catenin in the cytoplasm and nucleus is prevented by its interaction with the protein complex formed from the tumour-suppressor gene product APC, glycogen synthase kinase 3 $\beta$  (GSK-3 $\beta$ ) and the scaffolding protein Axin, which phosphorylate  $\beta$ -catenin and drive it into

ubiquitin-proteasome mediated degradation. In this “ $\beta$ -catenin destruction complex”, the GSK-3 $\beta$  component catalyses the phosphorylation of serine and threonine residues in the NH<sub>2</sub>-terminal domain of the  $\beta$ -catenin. The phosphorylated  $\beta$ -catenin is then recognised by a ubiquitin ligase complex, which targets it for degradation and downregulation by the proteasome.<sup>21,22,23</sup>



**Scheme 1.8** The Wnt/APC/ $\beta$ -catenin/TCF-4 signalling pathway

GSK-3 $\beta$  is inactivated by the Wnt class of secreted glycoproteins.<sup>24</sup> Active Wnt signalling thus leads to the up-regulation and accumulation of free cytosolic  $\beta$ -catenin. The free hypophosphorylated  $\beta$ -catenin subsequently moves to the nucleus where it forms a functionally active complex with members of the TCF (T-cell factor) family of transcription

factors. These  $\beta$ -catenin-TCF complexes initiate transcriptional activation of a wide range of oncogenes. Without this complex formation, TCFs do not initiate transcriptional activation.

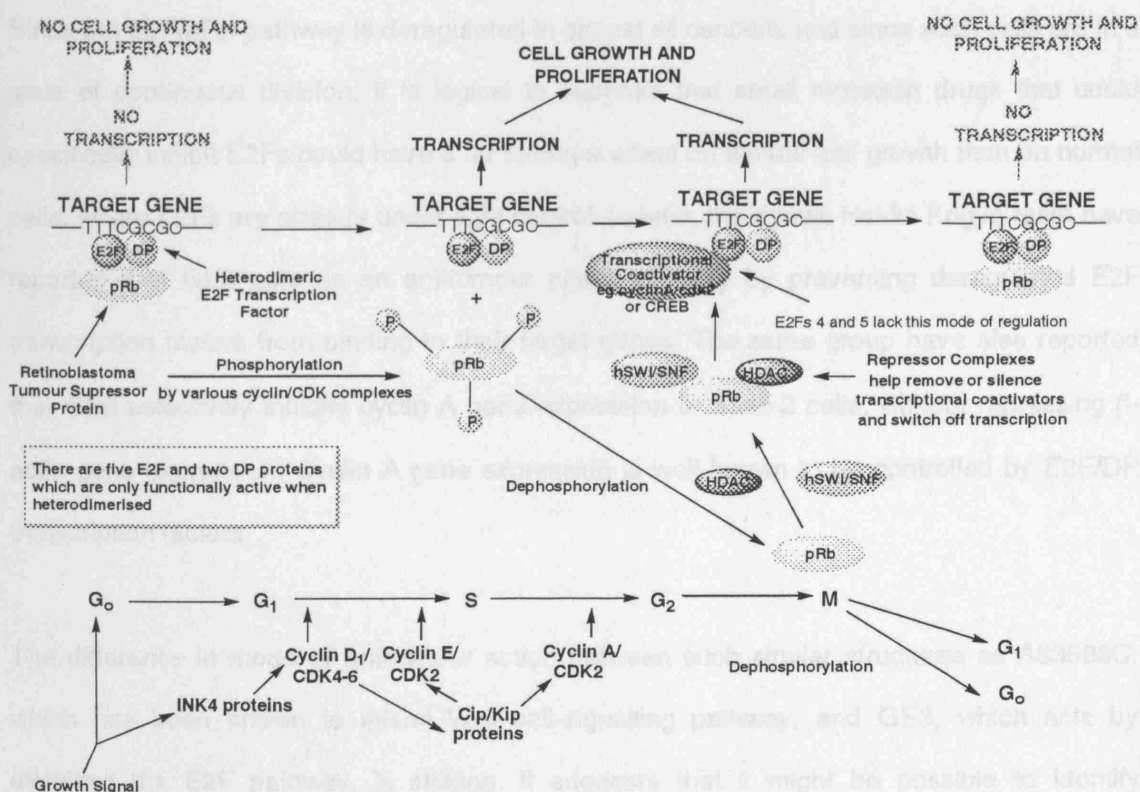
Mutation of the APC suppressor protein has been found to occur in approximately 80% of all sporadic colon cancers. Mutant APC proteins lose their ability to form the " $\beta$ -catenin destruction complex", which causes accumulation of  $\beta$ -catenin, formation of  $\beta$ -catenin-TCF complexes, and consequential activation of the TCF-transcription pathway and tumour cell growth. Mutations to the  $\beta$ -catenin gene can give rise to mutant forms of  $\beta$ -catenin that are resistant to the " $\beta$ -catenin destruction complex" but which are still effective at activating TCF-promoters. This mechanism has been found to be a cause of prostate cancers, gastric and pancreatic cancers, endometroid ovarian carcinomas, and melanomas.

As a consequence, it is now thought that up-regulation of  $\beta$ -catenin signalling is an important event in the onset of a variety of cancers. Small molecule drugs that could oppose the effects of  $\beta$ -catenin accumulation could have considerable potential as anti-cancer agents. A83586C is currently the most potent small molecule lead with proven effectiveness in this capacity. Collaborative studies between the Hale group and Novartis have recently shown that synthetic A83586C inhibits the TCF4 promoter in a HCT-116 human colon tumour cell line at an  $IC_{50}$  of 40 nM; significantly, A83586C also inhibits the growth of such cells at an identical concentration.

### 1.3 The E2F signalling pathway

E2F transcription factors are heterodimeric proteins composed of one E2F and one DP protein. They are essential for normal progression through the cell cycle. Six E2F genes and two DP genes have so far been identified. The E2F-DP heterodimers are regulated in normal cells by their association with tumour-suppressing pocket proteins, which include the retinoblastoma protein (pRb), p107 and p130.<sup>25</sup>

In normal cells, pRb is hypophosphorylated in the  $G_0$  and  $G_1$  stages of the cell cycle, and it is able to bind to E2F-DP heterodimers. This inhibits their transcriptional activation capacity at this stage. As the cell approaches the late  $G_1$  phase of the cell cycle, the Rb family of proteins become phosphorylated (Scheme 1.9). This process is controlled by the cyclins and their associated cyclin-dependent kinases (cyclins D1/CDKs 4-6 and cyclin E/CDK2), and causes the release of the free E2F-DP heterodimer. This then binds to one of the promoter regions of E2F-regulated genes via specific nucleotide sequences, resulting in the transcription of genes necessary for S-phase entry and cellular proliferation. pRb phosphorylation is maintained by cyclin A/CDK2 until mitosis, at which point dephosphorylation occurs. Genes activated by E2F-DP proteins include those encoding for proteins that play major roles in DNA replication (e.g. dihydrofolate reductase, DNA-polymerase  $\alpha$ , thymidine kinase) and cell proliferation (e.g. cyclins A/E, E2F1 and E2F2, cdc-2). The promoters of these genes contain consensus sequences that bind E2F complexes.



**Scheme 1.9** The pRb/E2F Signalling Pathway



Uncontrolled E2F activity can be caused by many cell cycle gene alterations, such as overexpression of cyclin D1 and cdk4, and the mutation or deletion of the cyclin-dependent kinase inhibitor (CDKI), as is frequently the case in tumour cells. The Rb gene is also often mutated in tumour cells, with most pRb gene mutations resulting in unstable retinoblastoma proteins that are unable to bind E2F-DP complexes. Such mutations have now been identified in a wide spectrum of tumours including osteosarcomas, small cell lung carcinomas, breast carcinomas and others. Certain viral oncoproteins, such as the human papillomavirus E7 protein, can bind to (and thus inactivate) functional pRb and cause tumour development. Indeed, there seems to be an alteration of at least one component of the E2F/Rb pathway in virtually all forms of cancer. These alterations generally lead to increased expression of transcriptionally active E2F, causing continuous expression of target genes whose products promote cell cycle progression. This can result in either oncogenic transformation or apoptosis.

Since the E2F/pRb pathway is deregulated in almost all cancers, and since such cells are in a state of continuous division, it is logical to suppose that small molecule drugs that could specifically inhibit E2Fs could have a far stronger effect on tumour cell growth than on normal cells, where E2Fs are already under tight control. Indeed, the Kyowa Hakko Kogyo team have reported that GE3 acts as an antitumour agent primarily by preventing deregulated E2F transcription factors from binding to their target genes. The same group have also reported that GE3 selectively inhibits cyclin A gene expression in Saos-2 cells, without repressing  $\beta$ -actin gene expression. Cyclin A gene expression is well known to be controlled by E2F/DP transcription factors.

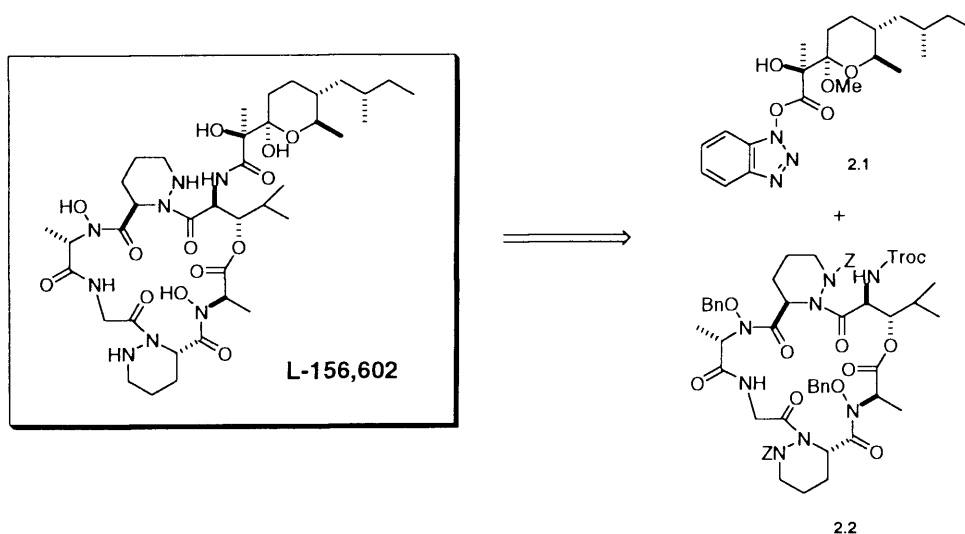
The difference in mode of antitumour action between such similar structures as A83586C, which has been shown to inhibit Wnt cell-signalling pathway, and GE3, which acts by inhibiting the E2F pathway, is striking. It suggests that it might be possible to identify analogues that will act on either pathway individually, or on both pathways simultaneously. The simultaneous inhibition of two deregulated cell signalling pathways by a single “small

molecule" drug is most attractive as it could lead to an even more effective cancer treatment, as it is often the case that more than one signalling pathway is malfunctioning.

## Chapter 2 Previous synthetic studies on the azinothricin family

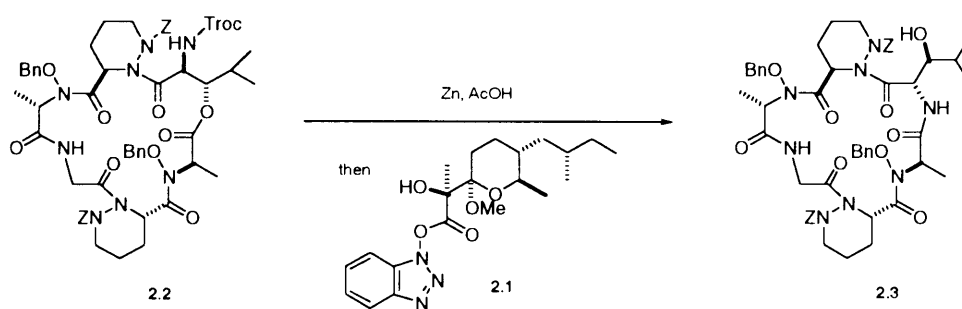
### 2.1 Total synthesis of L-156,602

L-156,602 was synthesised in 1990 by a team led by Caldwell and Durette at Merck Sharp and Dohme Research Laboratories.<sup>13</sup> The structure of L-156,602 consists of a complex cyclodepsipeptide motif linked to a lipophilic tetrahydropyranyl side chain via an amide bond. The peptide backbone is comprised of glycine and five unusual amino acids: (*R*)- and (*S*)-piperazic acids, (*R*)- and (*S*)-*N*-hydroxy-L-alanine and (2*S*,3*S*)-3-hydroxy-L-leucine. The Merck team thus required efficient synthetic routes to all of these amino acid residues, as well as a strategy for coupling them together in the formation of the cyclodepsipeptide via an appropriately functionalised hexadepsipeptide. Their initial retrosynthetic plan (Scheme 2.1) involved the coupling of fully protected cyclodepsipeptide **2.2** with activated ester **2.1**.



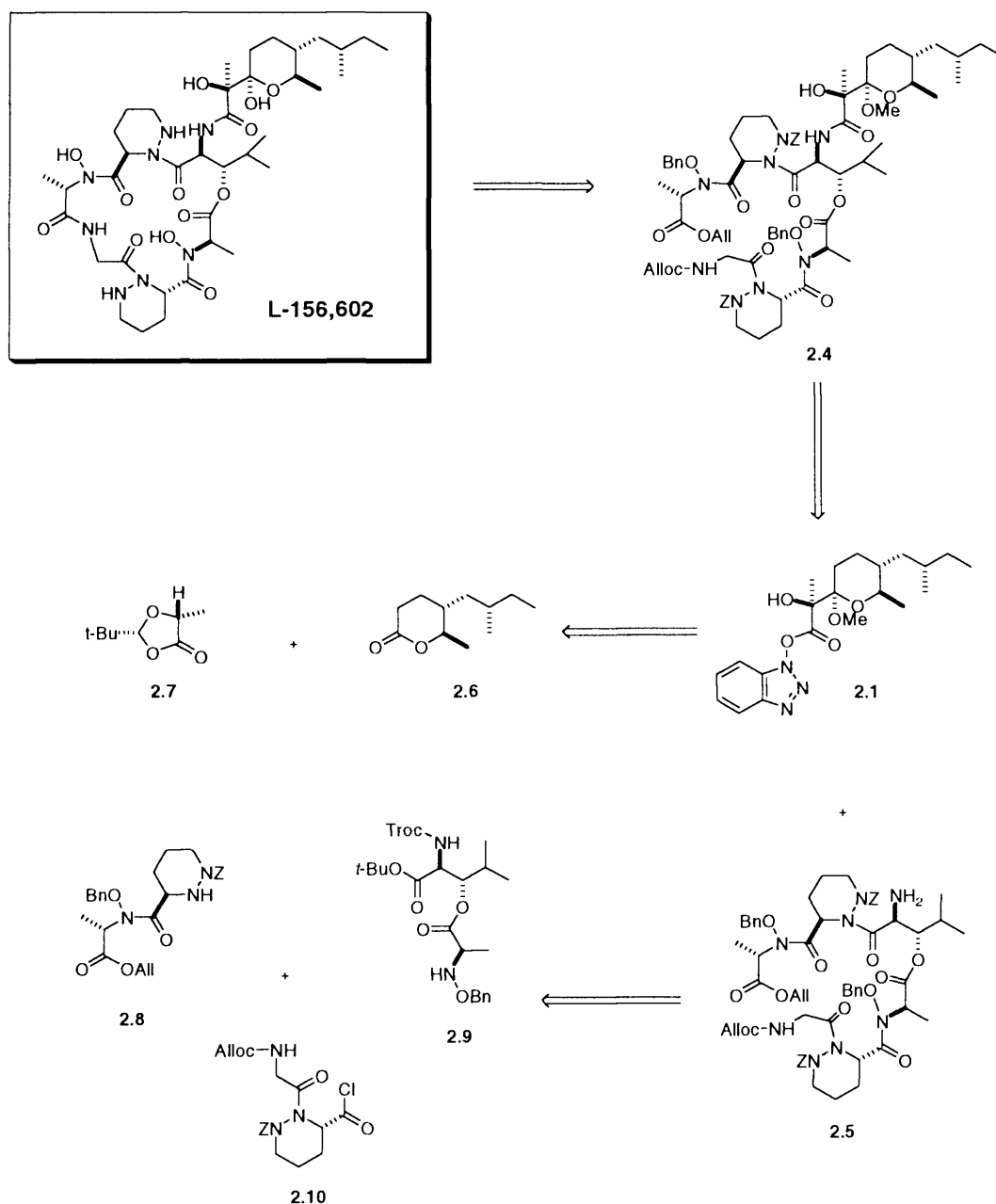
**Scheme 2.1** Merck's initial retrosynthetic analysis of L-156,602

However, this approach was thwarted at a late stage when the free amine formed by reductive removal of the Troc protecting group from **2.2** underwent an *O,N*-acyl shift in preference to amidation with activated ester **2.1** (Scheme 2.2).



**Scheme 2.2** O, N-acyl rearrangement of cyclodepsipeptide **2.2**

An alternative strategy which introduced the side chain at the linear hexadepsipeptide stage, as outlined in Scheme 2.3, was therefore developed by the Merck team. This plan involved formation of the cyclodepsipeptide of L-156,602 via cyclization of partially protected linear hexadepsipeptide **2.4**. The planned macrolactamisation between the *N*-benzyloxy-L-alanine and glycine residues was considered the most favourable possible ring-closure as it would involve the least hindered, most nucleophilic nitrogen attacking the activated carbonyl. The key cyclisation substrate **2.4** could be formed via a coupling between activated ester **2.1** and hexapeptide **2.5**. The tertiary hydroxyl stereocentre of the pyran side chain of **2.1** could be constructed via condensation of Seebach's ester **2.7** with lactone **2.6**. Hexapeptide **2.5** would be assembled by a [2+2+2] fragment condensation between **2.8**, **2.9** and **2.10**.



**Scheme 2.3** Merck's revised retrosynthetic analysis of L-156,602

The Merck synthesis of the tetrahydropyranyl acyl side chain of L-156,602 commenced with a diastereoselective Frater-Seebach alkylation reaction<sup>26</sup> between the enolate derived from (*R*)-3-hydroxy-butanoate **2.11** and (*S*)-1-iodo-2-methylbutane **2.12** (Scheme 2.4). This gave alcohol **2.13**, which was protected as a TES-ether. Reduction of the methyl ester with DIBAL-H gave primary alcohol **2.14**, which was oxidized to aldehyde **2.15** under Swern conditions. Subsequent Wittig olefination, hydrogenation and *O*-desilylation steps gave lactone **2.6**.

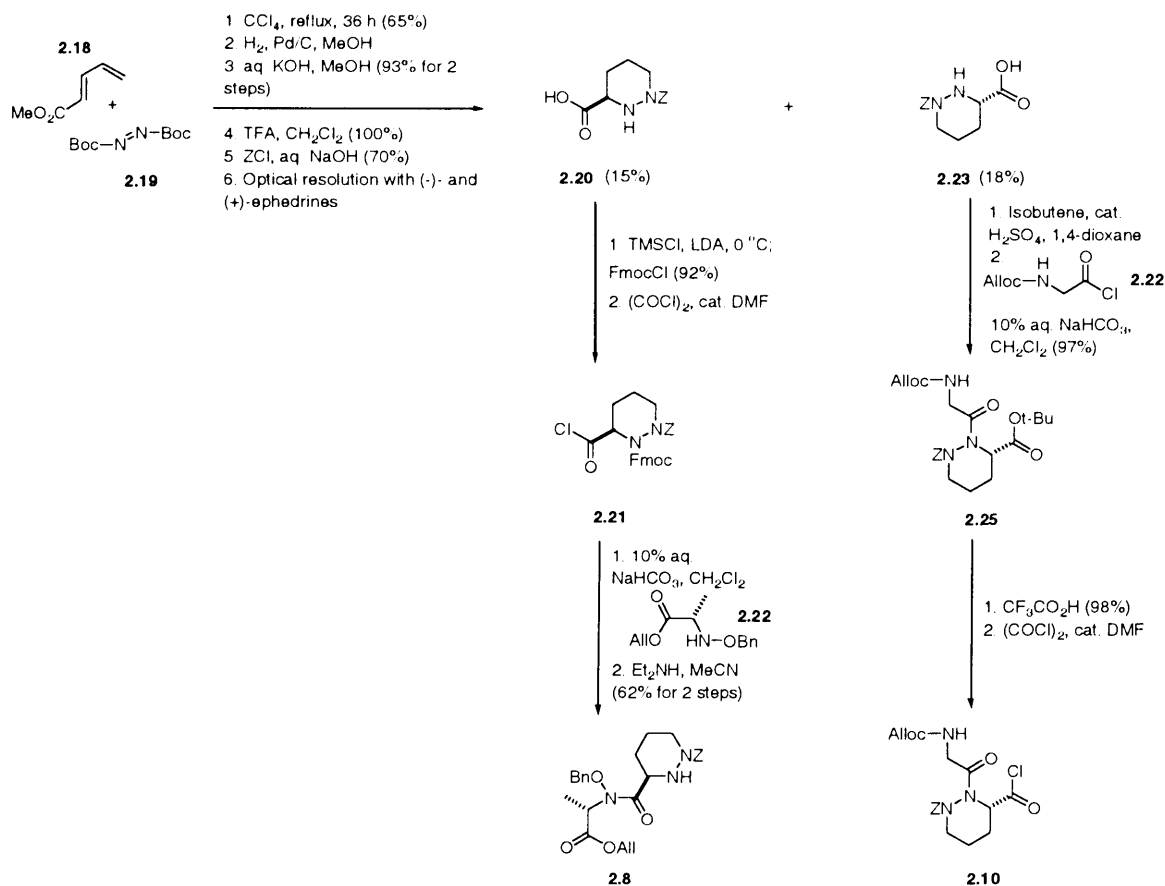


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Formation of the *N*(1)-*Z* derivative was followed by optical resolution with (+)- and (-)-ephedrine to give **2.20** and **2.23** in 15% and 18% respectively.<sup>29</sup> Acid **2.20** was converted into acid chloride **2.21**, which was subjected to a Carpino<sup>30</sup> biphasic coupling with *N*-benzyloxy-L-alanine derivative **2.22** to give, after removal of the Fmoc protecting group, dipeptide **2.8**.

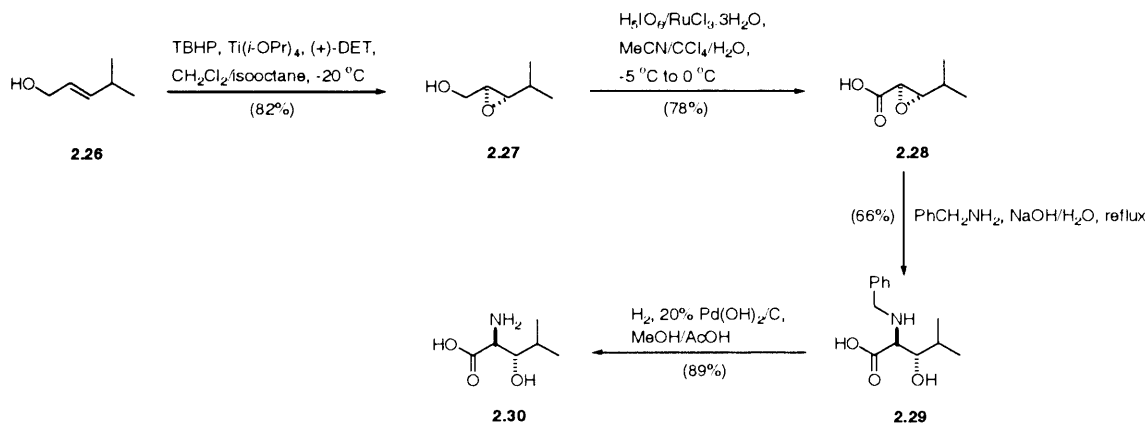


**Scheme 2.5** Synthesis of dipeptides **2.8** and **2.10**

A similar Carpino biphasic amino acid coupling between (*S*)-piperazic acid derivative **2.23** and acid chloride **2.24** was employed in the synthesis of dipeptide **2.25**, which was then transformed into acid chloride **2.10** in two steps.

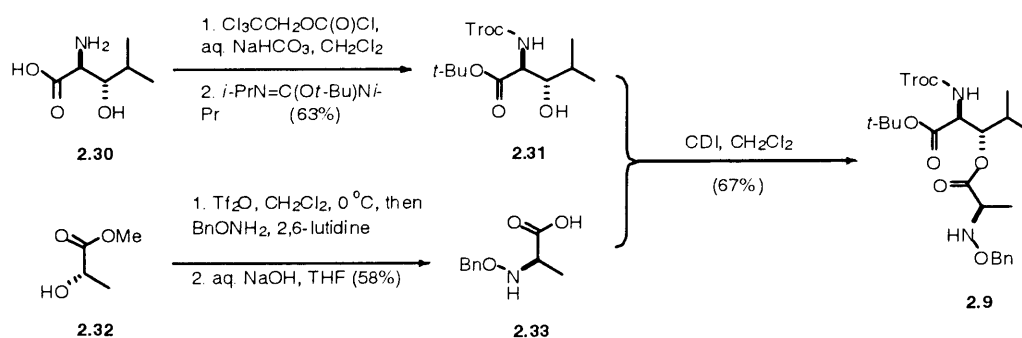
Scientists at Merck had previously reported a convenient synthesis of (2*S*,3*S*)-3-hydroxyleucine, **2.30**.<sup>31</sup> As outlined in Scheme 2.6, their route utilized a Sharpless asymmetric epoxidation of allylic alcohol **2.26** to furnish epoxide **2.27** in 95% ee. Oxidation to carboxylic

acid **2.28** was followed by regioselective epoxide opening with benzylamine to give *N*-benzyl derivative **2.29**. Hydrogenolysis of this intermediate completed their efficient route to **2.30**.



**Scheme 2.6** Merck's synthesis of (2*S*,3*S*)-3-hydroxyleucine

With (2*S*,3*S*)-3-hydroxyleucine in hand, the Merck team were able to execute a synthesis of depsipeptide **2.9**, the third and final dipeptide required by their [2+2+2] fragment condensation strategy. Chemoselective protection of **2.30** gave **2.31**, which was coupled with *N*-benzyloxyalanine **2.33** to give **2.9** in 67% yield with 1,1'-carbonyldiimidazole as the electrophilic activator (Scheme 2.7).

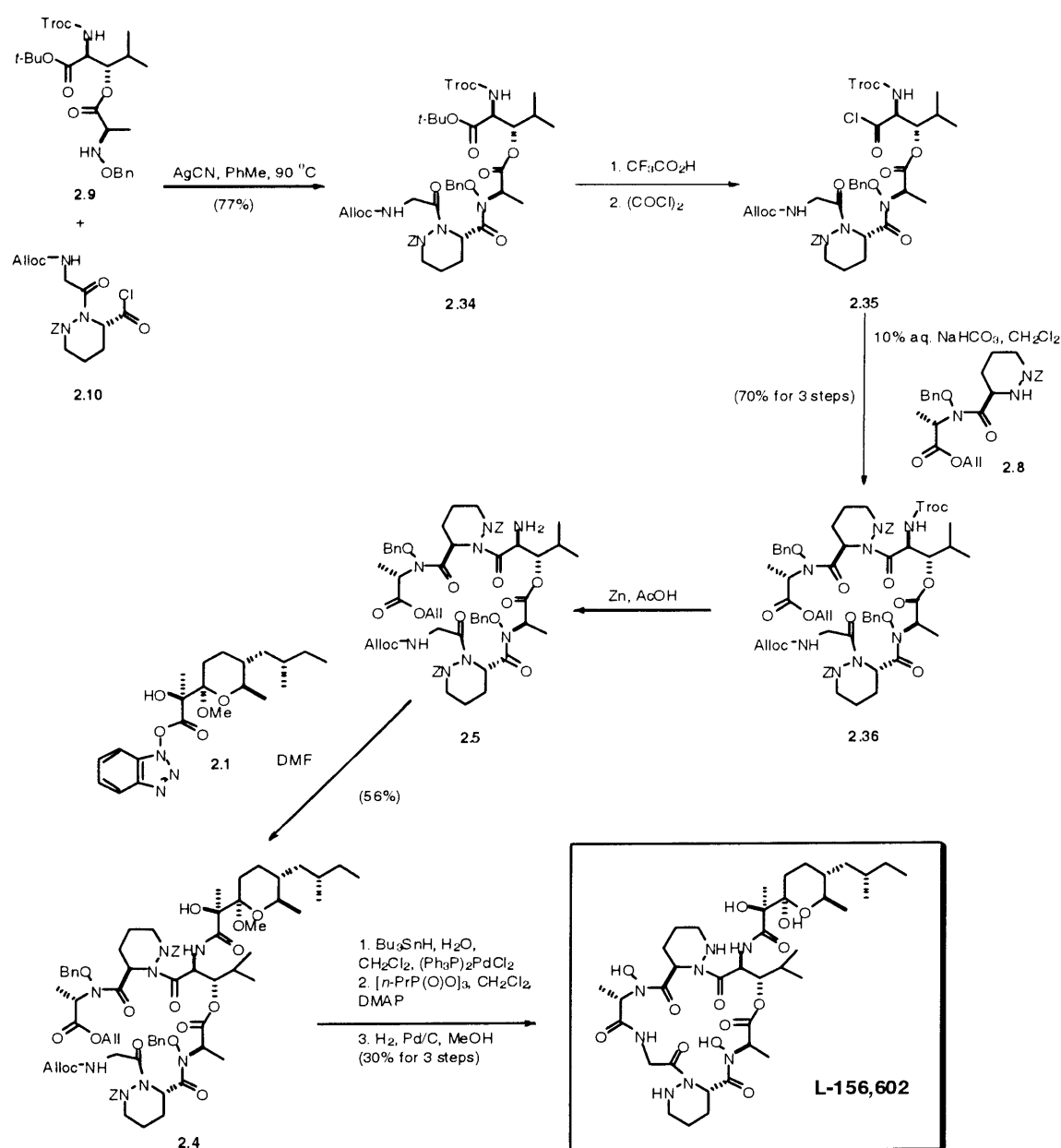


**Scheme 2.7** Synthesis of dipeptide **2.9**

The synthesis continued with a AgCN-mediated amidation reaction between depsipeptide **2.9** and acid chloride **2.10** (Scheme 2.8). Cleavage of the *t*-butyl ester group of the derived



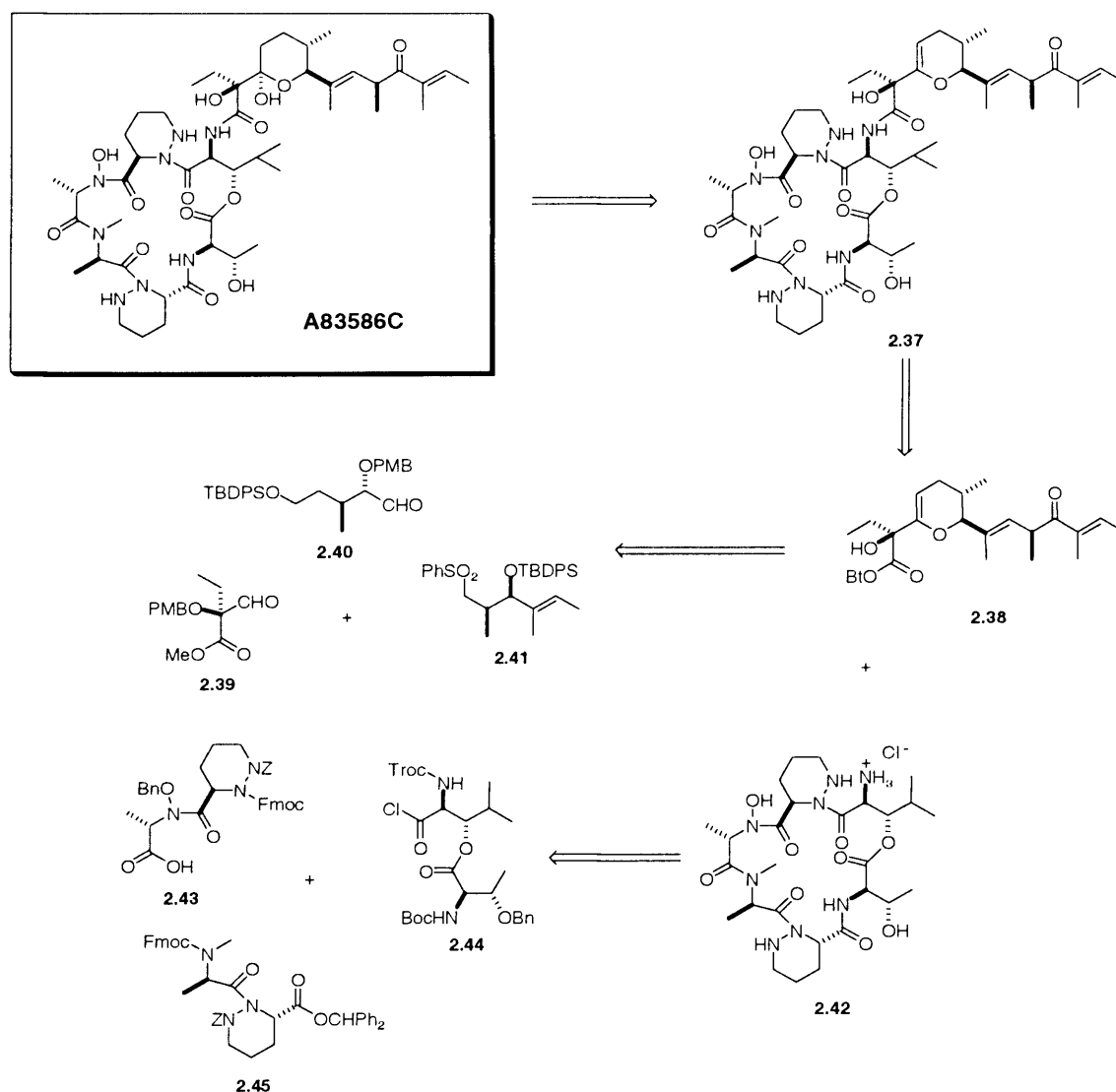
tetradepsipeptide **2.34** gave a carboxylic acid which was converted into acid chloride **2.35**. A Carpino coupling between **2.35** and **2.8** then gave Troc-protected linear hexadepsipeptide **2.36**. Reductive removal of the Troc protecting group with Zn dust unveiled the free amine of **2.5**, which underwent *N*-acylation with activated ester **2.1** in DMF in 56% yield. Pd(0)-catalysed hydrostannolysis<sup>32</sup> of the terminal *O*-allyl groups of **2.4** gave the macrolactamisation precursor, which was activated to ring closure using *n*-propane phosphonic anhydride<sup>33</sup> and DMAP.



Scheme 2.8 Synthesis of L-156,602

A final global hydrogenolytic deprotection of the cyclisation product removed the Z and Bn protecting groups to give L-156,602 in 53% yield, thus completing the Merck team's landmark synthesis of this natural product.

## 2.2 Total synthesis of A83586C

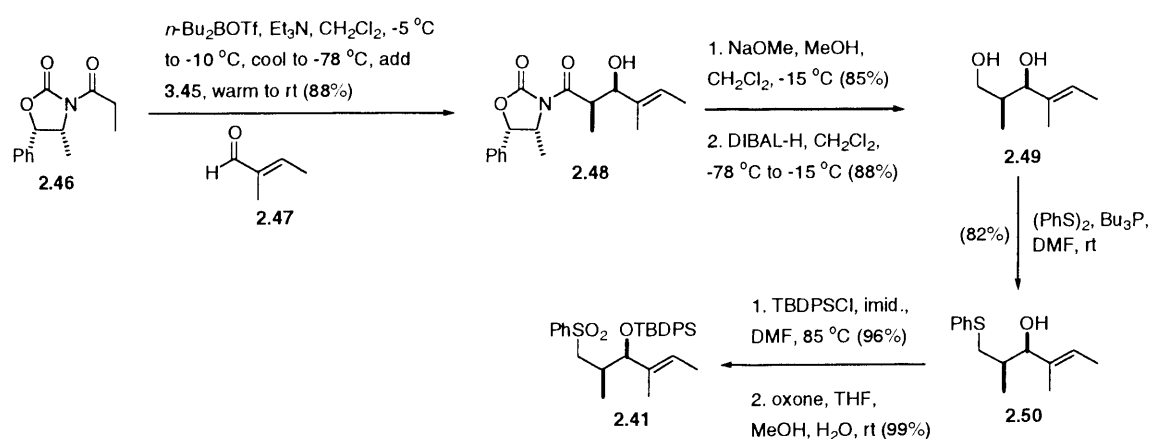


**Scheme 2.9** Hale's retrosynthetic analysis of A83586C

The total synthesis of A83586C was first accomplished by the Hale group in 1997.<sup>34</sup> In contrast to the Merck synthesis of L-156,602, Hale's route to A83586C was based on a highly

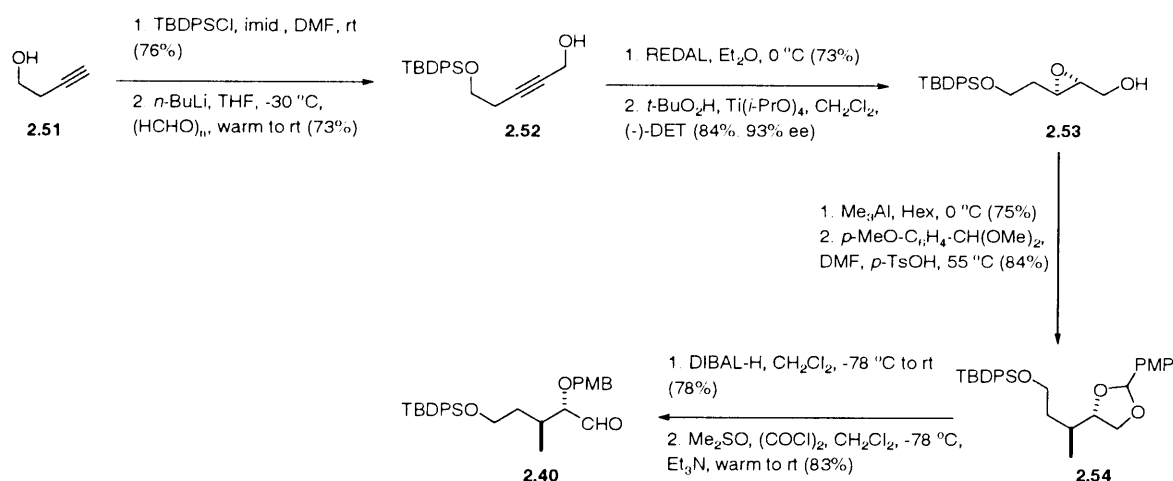
chemoselective coupling strategy which avoided the use of heteroatom protecting groups throughout the final steps. The key reaction was planned to be a biomimetic coupling between activated ester **2.38** and a fully deprotected cyclodepsipeptide salt **2.42** (Scheme 2.9). The resultant glycal **2.37** was expected to undergo stereoselective hydration under mild acidic conditions to give the natural product. This bold endgame was deemed necessary as the target's lability to acids, bases, oxidizing agents and reducing agents effectively ruled out conventional protecting group strategies for the completion of the synthesis. The pyran side chain was disconnected to give sulfone **2.41** and aldehydes **2.39** and **2.40** as key intermediates, while the cyclodepsipeptide portion was deemed to be accessible from a [2+2+2] fragment condensation strategy involving dipeptides **2.43**, **2.44** and **2.45**.

Sulfone **2.41** was constructed in 6 steps from enantiopure propionamide **2.46**, with an asymmetric *syn*-aldol reaction<sup>64</sup> between tiglic aldehyde **2.47** and the *Z*-boron enolate of **2.46** being used to set the two stereocentres of the molecule (Scheme 2.10). The resultant aldol adduct **2.48** was obtained as a crystalline solid, and was converted into alcohol **2.49** via transesterification and methyl ester reduction steps. Selective thioetherification with diphenyl disulfide and tri-*n*-butylphosphine then gave **2.50**, which was protected and oxidized to give the desired sulfone **2.41** in 50% yield for the whole sequence.



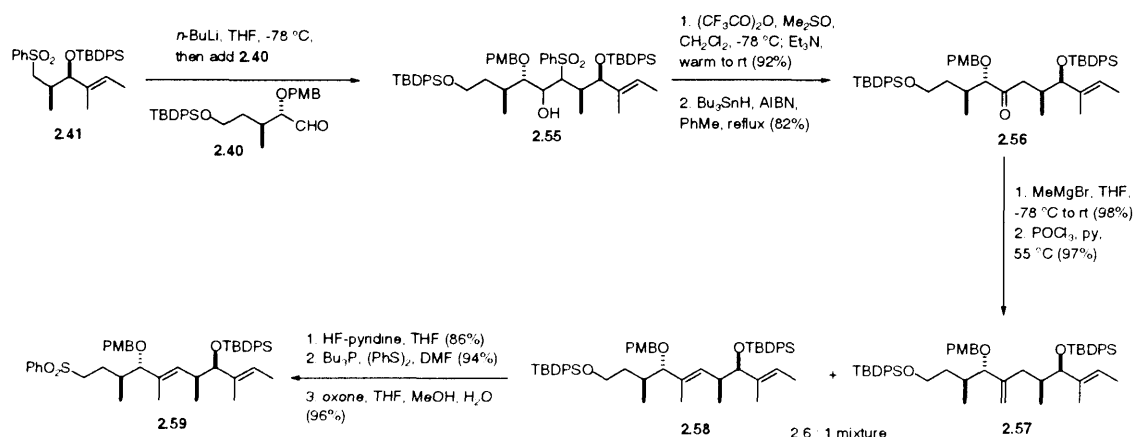
**Scheme 2.10** Synthesis of sulfone **2.41**

The key step in the synthesis of aldehyde **2.40** was a Sharpless asymmetric epoxidation of the allylic alcohol derived from selective reduction of alkynol **2.52** (Scheme 2.11). The resulting chiral epoxide<sup>35</sup> **2.53** underwent a highly regio- and stereoselective ring-opening reaction with trimethylaluminium to furnish a 1,2-diol, which was protected as a *p*-methoxybenzylidene acetal. Regioselective reductive opening<sup>36</sup> of acetal **2.54** with DIBAL-H positioned the PMB protecting group on the secondary oxygen atom, thus creating a primary alcohol group which was oxidized to aldehyde **2.40** under Swern conditions.

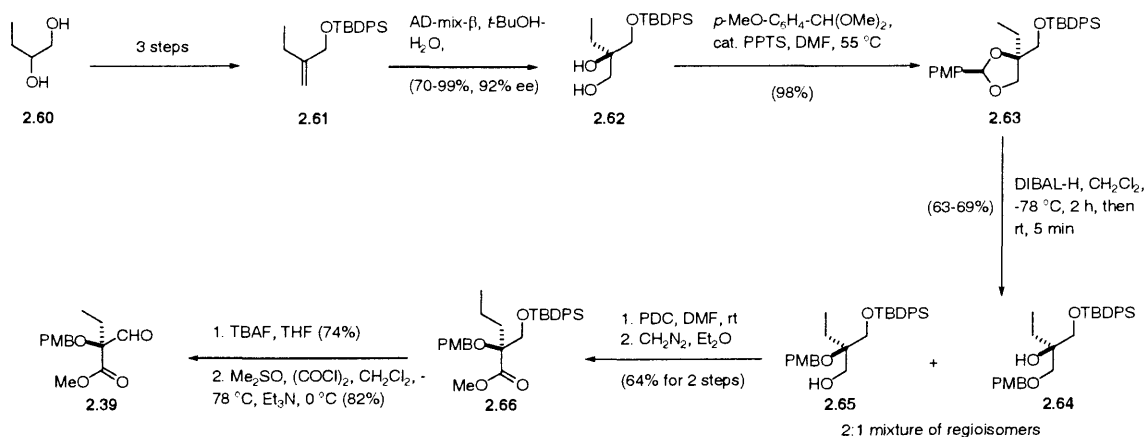


**Scheme 2.11** Synthesis of aldehyde **2.40**

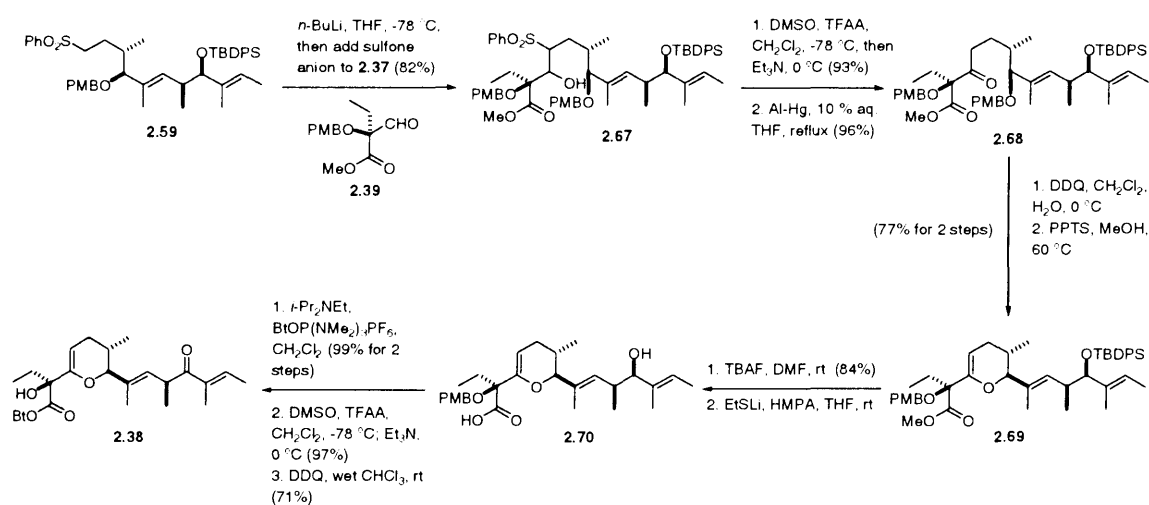
The Hale synthesis proceeds with addition of the lithium anion of sulfone **2.41** to aldehyde **2.40** to furnish  $\beta$ -hydroxysulfone **2.55** as a mixture of four diastereomers (Scheme 2.12). Subsequent Swern oxidation and desulfonylation via Smith's tri-*n*-butylstannane radical method<sup>37</sup> gave ketone **2.56** as a single compound. Although conversion of this ketone into the *Z*-enol triflate was facile, all attempts at transforming this intermediate into **2.58** using the Stille<sup>81</sup> or McMurry-Scott<sup>38</sup> cross-coupling protocols were unsuccessful. An alternative tactic was therefore required, and this involved addition of methylmagnesium bromide to the ketone, followed by POCl<sub>3</sub>-pyridine-mediated dehydration to give a 2.6:1 mixture of alkene products **2.58** and **2.57**. Chromatographic purification of the desired isomer was conducted after selective removal of the terminal TBDPS protecting groups with HF.pyridine. Thioetherification and oxidation steps completed the route to sulfone **2.59**.

Scheme 2.12 Synthesis of sulfone **2.59**

The asymmetric synthesis of aldehyde **2.39** was founded on a Sharpless asymmetric dihydroxylation reaction<sup>39</sup> of alkene **2.61**, which gave diol **2.62** in high yield and 92% ee (Scheme 2.13). A *p*-methoxybenzylidenation / acetal reduction tactic was again used to place a PMB protecting group on the more hindered hydroxyl of the diol. However, the regioselectivity of the DIBAL-H reduction was not high, a 2:1 mixture of alcohols **2.64** and **2.65** being formed. These isomers were separated by flash chromatography, and the desired alcohol was converted into ester **2.66** by oxidation with PDC and esterification with diazomethane. Finally, aldehyde **2.39** was accessed following TBDPS-deprotection and Swern oxidation.

Scheme 2.13 Synthesis of aldehyde **2.39**

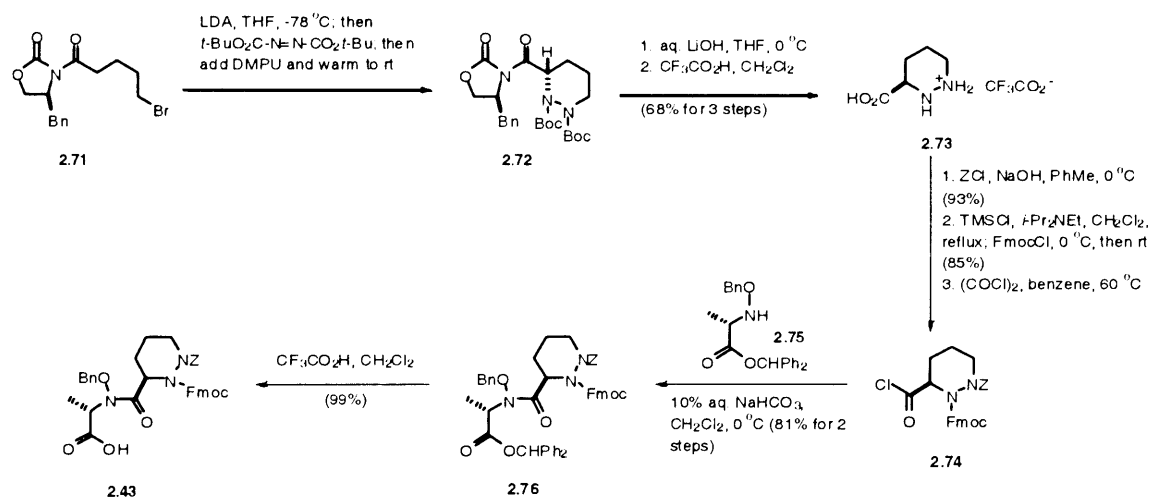
Unification of **2.59** and **2.39** was achieved by addition of the sulfone anion to aldehyde **2.39** according to Scheme 2.14. The resultant diastereomeric mixture of  $\beta$ -hydroxysulfones **2.67** was oxidized under Swern conditions and desulfonated via the aluminium amalgam reduction method of Corey-Chaykovsky<sup>40</sup> to form ketone **2.68**. Selective deprotection of the less hindered, secondary PMB-ether was conducted with DDQ (1.2 equiv.) in cooled aqueous  $\text{CH}_2\text{Cl}_2$ . This provided a mixture of the linear hydroxy-ketone and two ring-closed hemi-ketals. Dehydrative ring-closure with catalytic PPTS in methanol simplified this three-component system, furnishing glycal **2.69** in good yield. *O*-Desilylation of the remaining TBDPS-ether, followed by demethylation with ethanethiolate, gave carboxylic acid **2.70**. Treatment of this compound with Castro's BOP reagent installed the desired *N*-hydroxybenzotriazole ester motif in a reaction that was unaffected by the presence of an allylic secondary hydroxyl group. A Swern oxidation was used to form the terminal enone, and finally the tertiary PMB-ether was cleaved with excess DDQ in wet chloroform to give activated ester **2.38**.



**Scheme 2.14** Synthesis of activated ester **2.38**

An efficient route to functionalised enantiopure piperazic acid derivatives was required by the Hale group as part of their effort to the cyclodepsipeptide portion of A83586C. This challenge was met by the novel method of tandem electrophilic hydrazination-nucleophilic cyclization.<sup>41</sup> In this protocol, a bromovaleric acid derivative is tethered onto an Evans chiral oxazolidinone auxiliary, and an asymmetric electrophilic hydrazination is carried out at  $-78$  °C. The resultant

aza-anion is allowed to warm to room temperature in the presence of DMPU, allowing a facile ring-closure to furnish piperazic acid derivative **2.72** (Scheme 2.15). Hydrolysis of the oxazolidinone, followed by TFA-mediated removal of the Boc protecting groups, gave (3*S*)-piperazic acid **2.73** in good yield and high ee (>96%). Access to the (3*R*)-piperazic derivative is equally efficient.

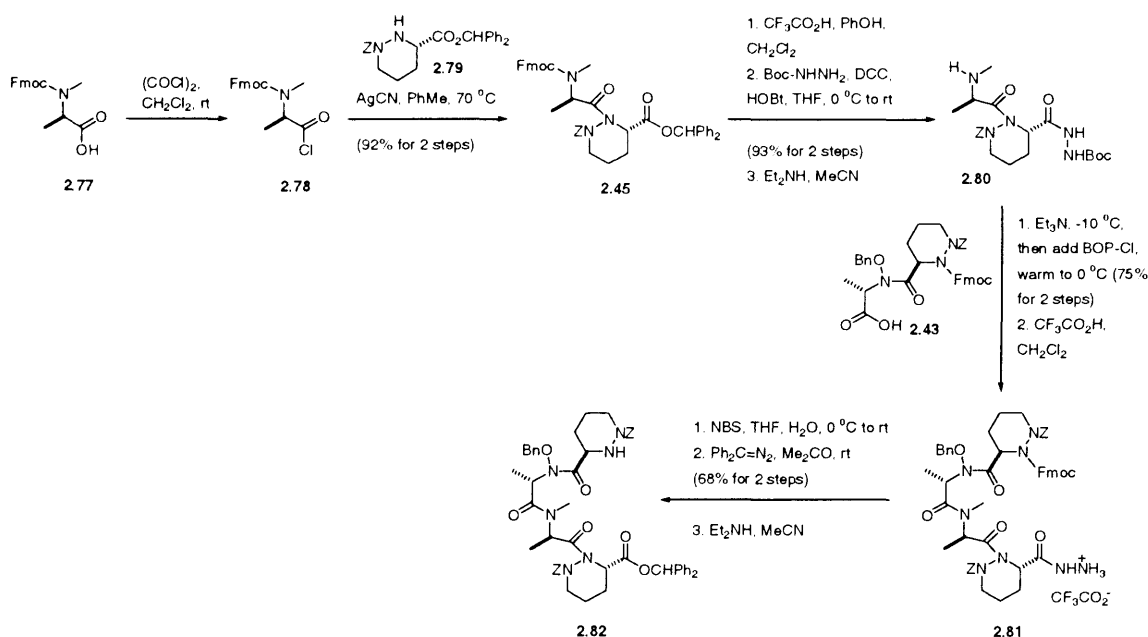


**Scheme 2.15** Synthesis of dipeptide **2.43**

Acid **2.73** was then modified to protected acid chloride **2.74**, which was subjected to a Carpino biphasic coupling with *N*-benzyloxy-L-alanine derivative **2.75** (Scheme 2.15). Dipeptide **2.43** was thus accessible on a large scale.

Hale's piperazic acid synthesis also allowed an expedient route to tetrapeptide **2.82** to be developed (Scheme 2.16). Acid chloride **2.78** (derived from the known Fmoc-protected alanine **2.77**) was coupled to piperazic acid derivative **2.79** with silver cyanide in toluene. The use of an acid chloride in this coupling was found to be essential due to the low nucleophilicity of the N(2) lone pair of **2.79**, which is deactivated by the N(1)-acyl group and also relatively hindered. The Fmoc amino-acid chloride was preferred to the  $\alpha$ -Boc or  $\alpha$ -Z-protected analogues due to ease of preparation and high reactivity (with minimal epimerization at the  $\alpha$ -stereocentre) of the Fmoc-protected substrate. Before removal of the Fmoc protecting group

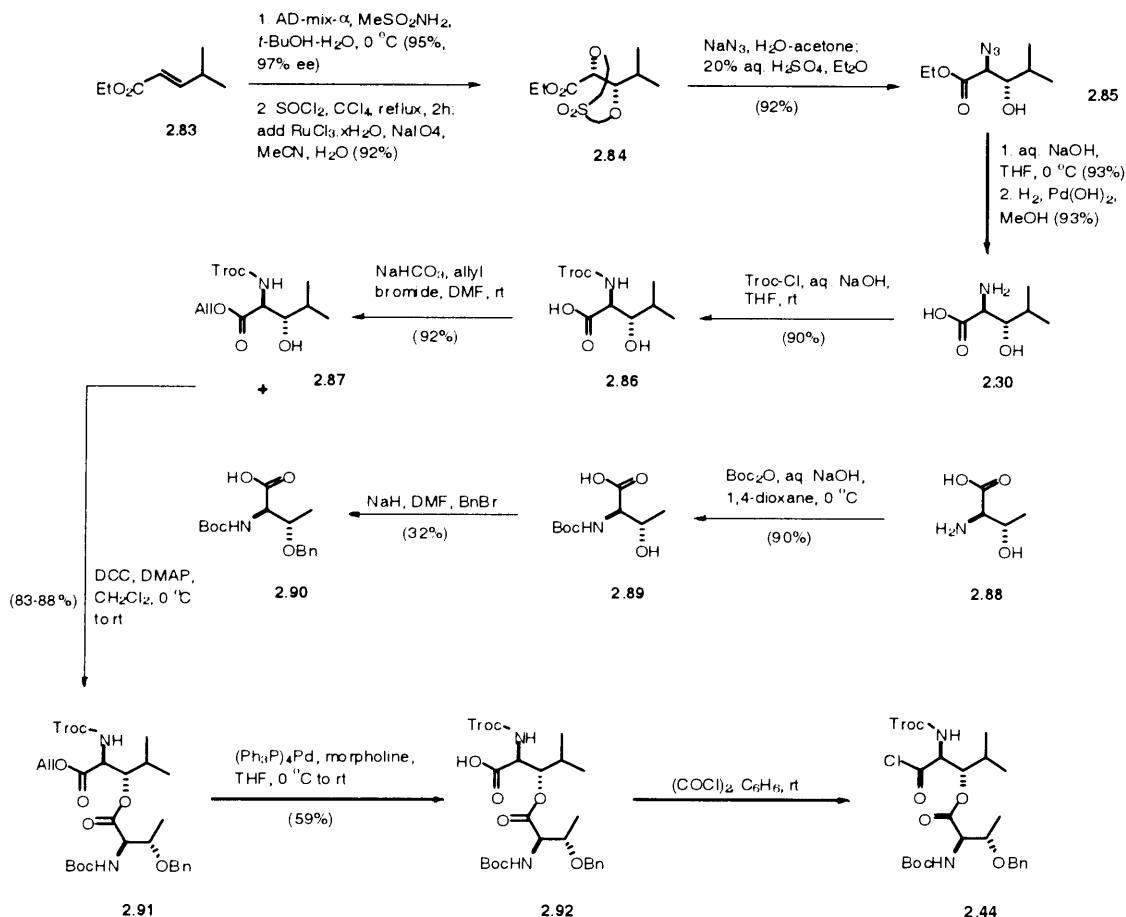
from **2.45**, it was found to be necessary to replace the diphenylmethyl ester group with a *tert*-butylcarbazide motif.<sup>42</sup> This allowed selective deprotection of the Fmoc group to give **2.80**. A [2+2] fragment condensation between **2.80** and **2.43** was then conducted, with BOP-Cl activation of the acid component. Removal of the Boc group with TFA gave **2.81**, which was treated with NBS<sup>43</sup> in THF-water to convert the acylhydrazine unit into an acid. Tetrapeptide **2.82** was then obtained following esterification of the carboxyl group with diphenyldiazomethane and base-assisted cleavage of the Fmoc protecting group.



**Scheme 2.16** Synthesis of tetrapeptide **2.82**

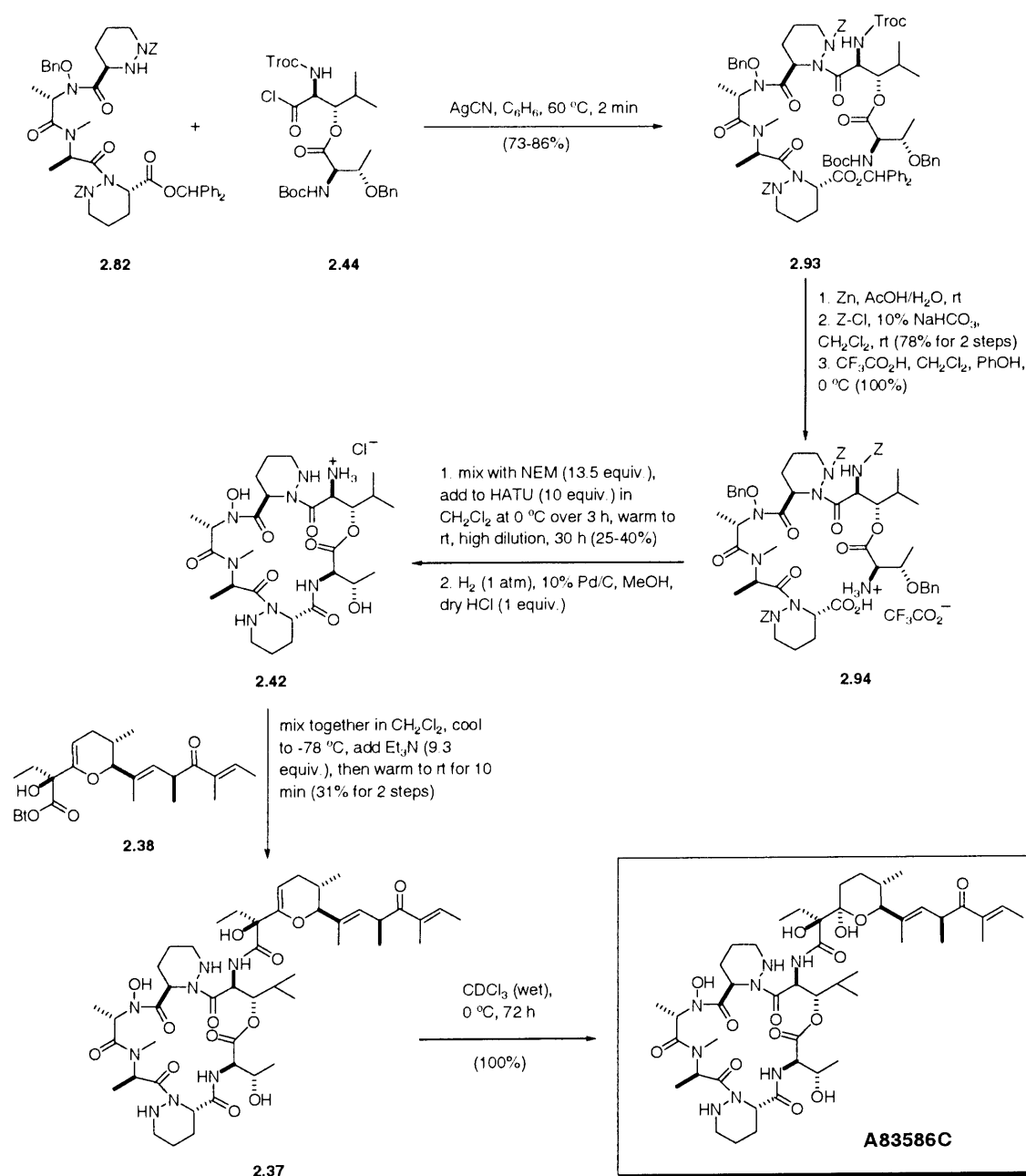
The Hale group also devised a new large-scale route to (2*S*,3*S*)-3-hydroxyleucine,<sup>44</sup> which was integral to their synthesis of depsipeptide **2.44**. Their six-step procedure relies upon Sharpless asymmetric dihydroxylation and Sharpless cyclic sulfate chemistry to install the *anti*-aminoalcohol motif in **2.30** (Scheme 2.17). (2*S*,3*S*)-3-Hydroxyleucine, so obtained, was transformed into **2.91** in a further three steps, with the depsipeptide being formed via a DMAP-assisted DCC coupling between **2.87** and **2.90**. Removal of the allyl protecting group with Pd(0) and morpholine, followed by chlorination with oxalyl chloride, then gave the depsipeptide acid chloride **2.44**.



Scheme 2.17 Synthesis of depsipeptide **2.44**

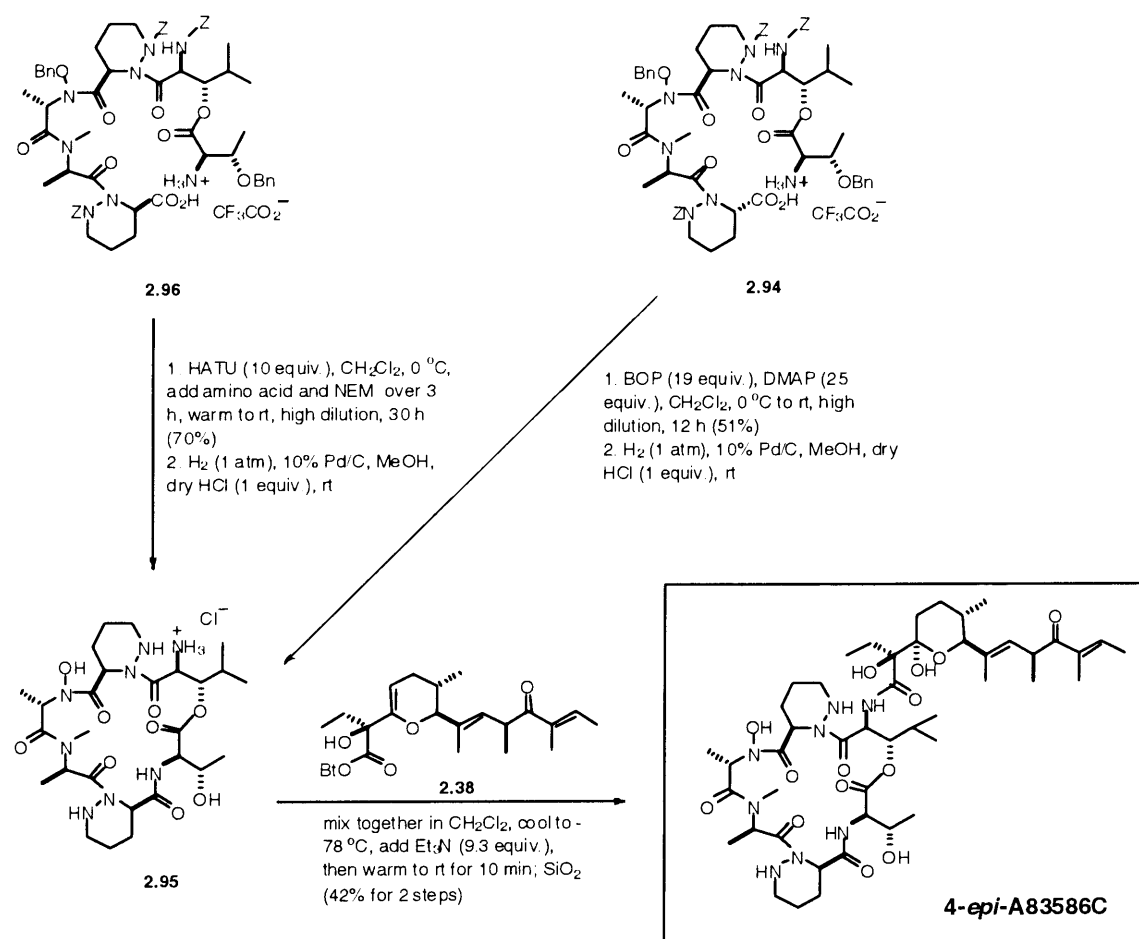
Hexadepsipeptide **2.93** was formed by careful AgCN-assisted amidation between **2.82** and **2.44**, with the reaction mixture being heated in benzene at  $60\text{ }^\circ\text{C}$  for only two minutes (Scheme 2.18). Further exposure of the reaction mixture to heat caused decomposition of **2.93**. The Troc protecting group was then replaced by a Z group, and the Boc and diphenylmethyl ester groups were selectively cleaved with TFA to furnish the key macrolactamisation pre-cursor **2.94**. After a screening of reagents for the ring-closure, only Carpino's HATU reagent<sup>45</sup> was found to promote the desired cyclization, delivering the product in 25-40% yield. Global deprotection of this material was then carried out via catalytic hydrogenolysis of the remaining Z and *O*-benzyl protecting groups. This hydrogenation was conducted over a Pd/C catalyst in methanolic HCl, with one equivalent of the acid being added to the reaction mixture to protonate the hydroxyleucine amine as soon as it was unveiled. This tactic ensured that *O*- to *N*-acyl migration did not occur in **2.42**. Finally, a highly

chemo- and regioselective coupling between the cyclodepsipeptide hydrochloride salt **2.42** and activated ester **2.38** was mediated by Et<sub>3</sub>N in CH<sub>2</sub>Cl<sub>2</sub> to give glycal **2.37** in 31% yield. The glycal motif of **2.37** was then hydrated in a highly regio- and stereoselective manner by allowing the material to stand in wet CDCl<sub>3</sub> for 3 days, delivering A83586C in quantitative yield.



Scheme 2.18 Synthesis of A83586C

In an effort to improve the efficiency of the macrolactamisation step, the Hale group examined the use of BOP and DMAP in  $\text{CH}_2\text{Cl}_2$  to effect this reaction (Scheme 2.19). However, this reagent combination transformed hexapeptide **2.94** into an alternative, undesired product **2.95** in 51% yield.<sup>46</sup> Exposure of the hexapeptide to the new reaction conditions had caused complete epimerisation of the (*R*)-piperazic acid unit. Presumably, the enhanced basicity of DMAP, combined with the possible formation of acyl pyridinium intermediates, contributes to the ease of abstraction of the relevant proton. The fact that epimerisation had occurred at this precise location was confirmed unambiguously via an independent total synthesis of **2.96**, with cyclisation to hexapeptide **2.95** occurring in 70% yield under the original HATU high dilution conditions.

Scheme 2.19 Synthesis of 4-*epi*-A83586C

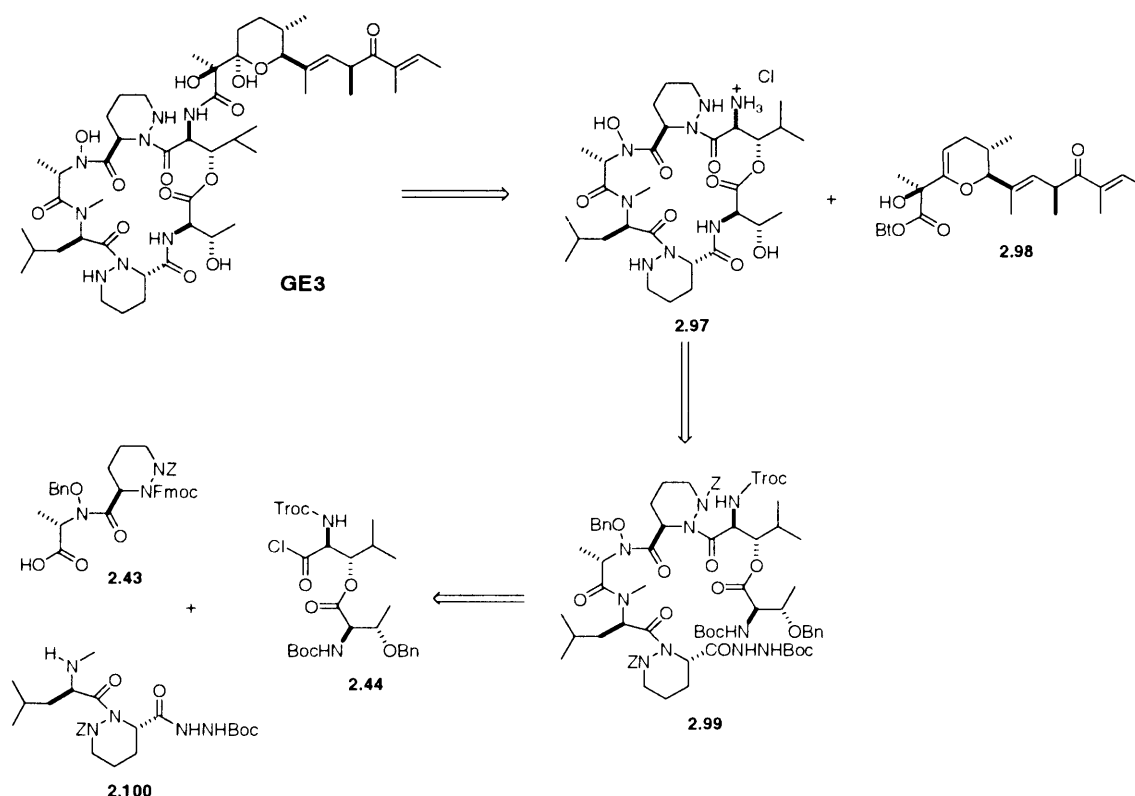
It is interesting to note the high yield for this macrolactamisation compared to the low yield (25%) observed for the original cyclisation of **2.94** in the A83586C synthesis. Thus, by merely inverting the stereochemistry of the terminal piperazic residue, the ease of cyclisation of the hexapeptide is drastically altered.

Although these BOP-mediated cyclisation studies did not lead to an improved route to A83586C, they did allow a synthesis of the novel analogue, 4-*epi*-A83586C<sup>46</sup> (Scheme 2.19), which provides further demonstration of the efficiency of the chemoselective BtO ester coupling strategy for assembling this class of molecule.

### 2.3 Synthetic studies towards GE3

Although a total synthesis of this natural product has not yet been achieved, considerable progress has been made towards it. In 2002 the Hale group published a synthesis of the GE3 cyclodepsipeptide,<sup>47</sup> and in the same year Hamada reported a route to a form of the acyl side chain segment.<sup>48</sup> Hale's retrosynthetic planning for GE3 (Scheme 2.20) was predicated upon the biogenetically inspired coupling of cyclodepsipeptide **2.97** with activated benzotriazole ester **2.98**. This strategy avoids the use of protecting groups throughout the endgame, which is similar to that employed in the successful A83586C synthesis described above.

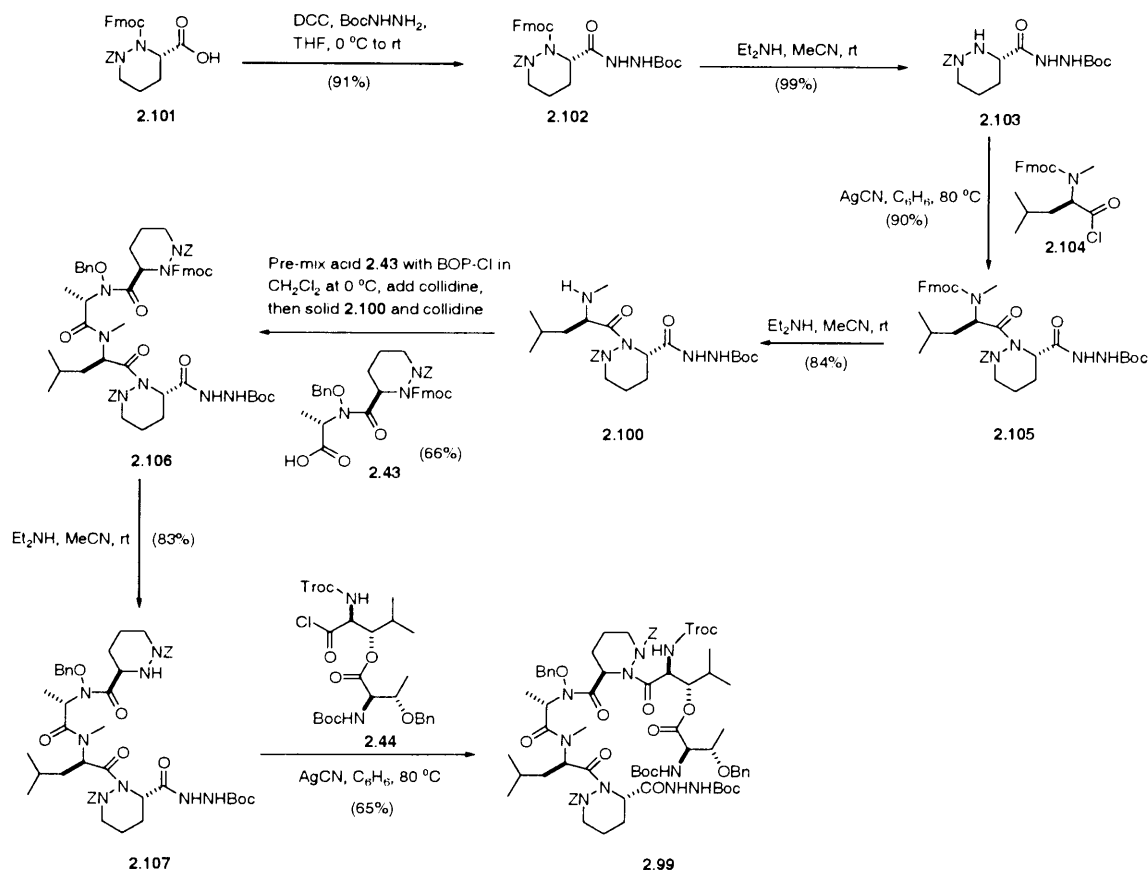
The GE3 cyclodepsipeptide core differs from that belonging to A83586C in one respect, namely the presence of an *N*-methyl-D-leucine residue in place of an *N*-methyl-D-alanine unit. Although this difference may seem trivial, synthetic studies in this area have shown (and continue to show) that minor changes in cyclodepsipeptide structure can exert dramatic effects on the reactivity, conformation and ease of formation of these molecules. The Hale group's proposed route to cyclodepsipeptide **2.97** was based on the [2+2+2] fragment condensation of dipeptides **2.43**, **2.44** and **2.100** (Scheme 2.20).



**Scheme 2.20** Hale's retrosynthetic analysis of GE3

Dipeptides **2.43** and **2.44** were previously synthesised during the Hale synthesis of A83586C, while dipeptide **2.100** was assembled in 4 steps from *N*(1)-*Z*-*N*(2)-Fmoc-piperazic acid **2.101**, which is itself readily available via Hale's tandem electrophilic hydrazination/nucleophilic cyclisation protocol (Scheme 2.21). The coupling of dipeptides **2.100** and **2.43** proved to be troublesome. A wide range of reaction conditions were found to be ineffective at mediating the desired amidation, including the BOP-Cl/Et<sub>3</sub>N system that had been applied successfully to the A83586C synthesis. After much scouting, the combination of BOP-Cl and collidine was discovered to effect the coupling, furnishing tetrapeptide **2.106** in 66% yield. Presumably, the greater steric bulk of collidine compared to Et<sub>3</sub>N helps to prevent it from initiating base-catalysed decomposition of the mixed anhydride derived from **2.43**. Use of Et<sub>3</sub>N as the base also caused significant Fmoc deprotection of the *N*-methyl-D-leucine fragment to occur. This was not a factor in the corresponding peptide coupling of the A83586C synthesis, which involved a less sterically hindered *N*-methyl-D-alanine dipeptide fragment. Removal of the

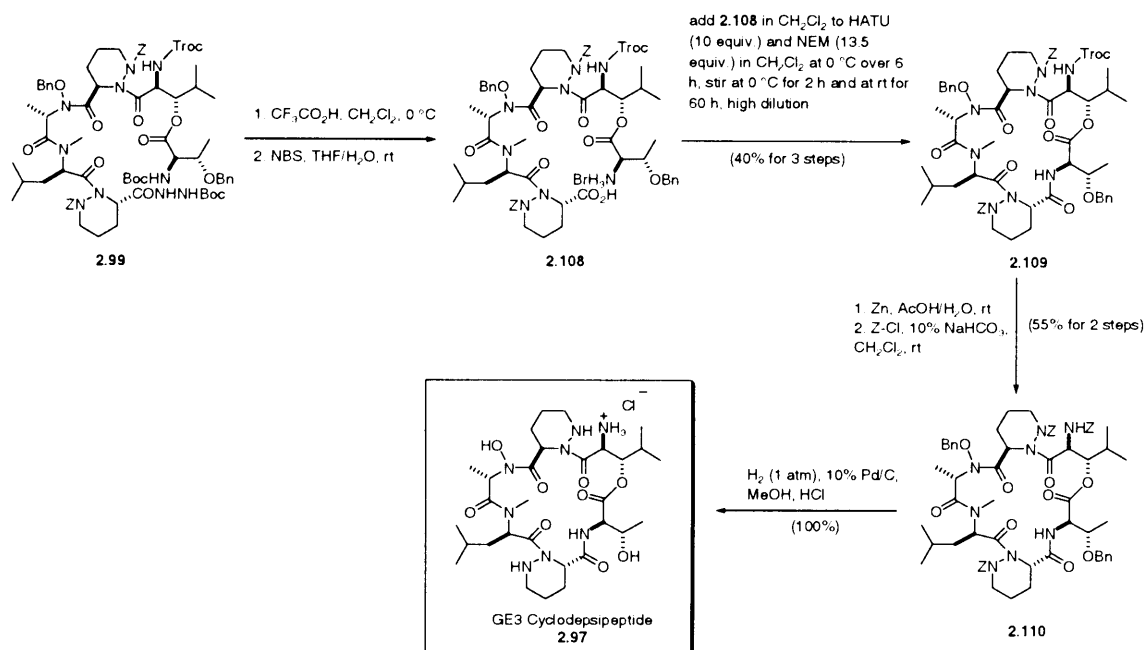
Fmoc group from **2.106** gave tetrapeptide **2.107**, thus paving the way for a silver cyanide-promoted [4+2] coupling with dipeptide **2.44** to give hexapeptide **2.99** in 65% yield.



### Scheme 2.21 Synthesis of hexapeptide **2.99**

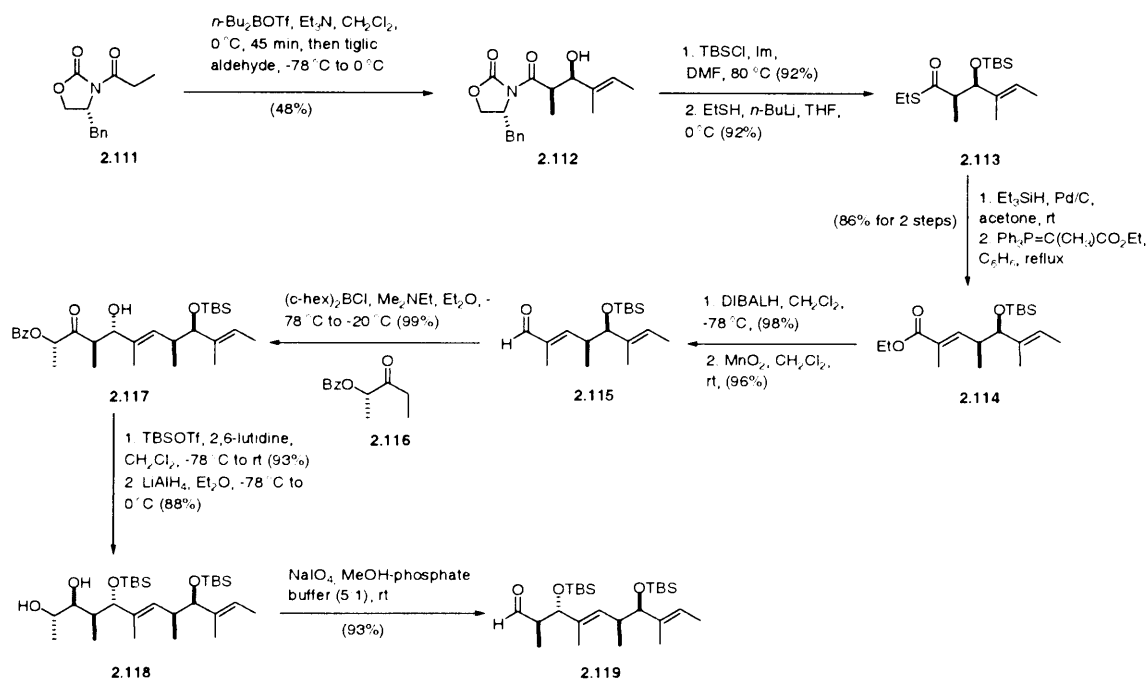
As a prelude to macrolactamisation, the two Boc groups were cleaved from **2.99** to give an *N*-acyl hydrazine, which was oxidized with NBS in THF to yield acid **2.108** (Scheme 2.22). A high dilution HATU-mediated cyclisation was then executed to give macrolactam **2.109** (40% yield from **2.99**). The corresponding A83586C macrolactamisation proceeded in significantly lower yield (25% for just the cyclisation), indicating that, in this case, the presence of the *N*-methyl-*D*-leucine residue has a positive effect on the reaction. The Troc group of **2.109** was deprotected with zinc dust in aqueous acetic acid, and the freed nitrogen was temporarily capped with a Z-group to ease purification of **2.110**. Finally, global deprotection of the remaining benzyl and Z-protecting groups by catalytic hydrogenation at atmospheric pressure over 10% Pd/C gave the GE3 cyclodepsipeptide in reasonably pure form. The hydrogenation

was executed in an acidic medium (methanol with one equivalent of HCl added) in order to prevent an *O*- to *N*-acyl shift from occurring in the  $\beta$ -hydroxyleucine residue.

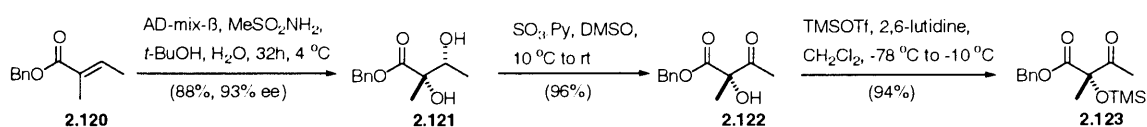


**Scheme 2.22** Synthesis of the GE3 cyclodepsipeptide

A stereoselective synthesis of the acyl side chain segment of GE3 was accomplished in 2002 by the Hamada group. The key sub-targets were aldehyde **2.119** and methyl ketone **2.123**, which were later unified via an aldol condensation. Their route to aldehyde **2.119** utilised an Evans *syn*-aldol reaction<sup>64</sup> and later a Paterson *anti*-aldol reaction<sup>49</sup> to set the stereocentres of this molecule (Scheme 2.23).

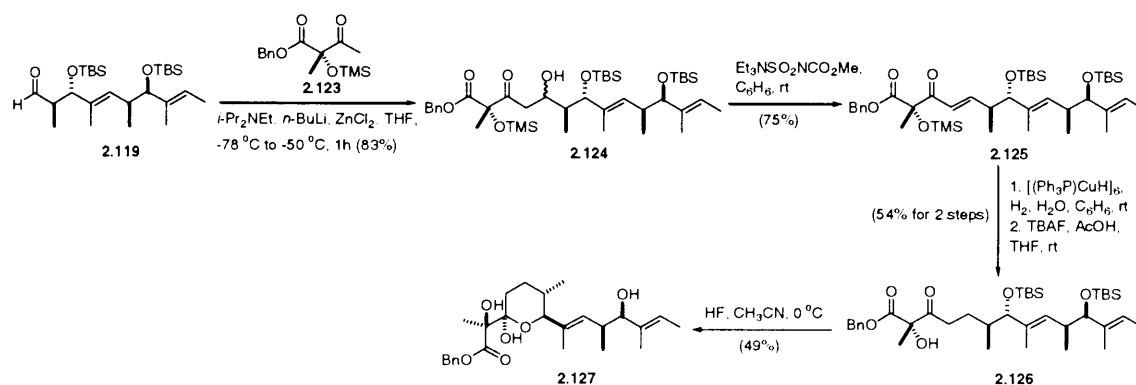
Scheme 2.23 Synthesis of aldehyde **2.119**

Hamada's route to methyl ketone **2.123** was founded on a Sharpless asymmetric dihydroxylation<sup>39</sup> of benzyl tiglate **2.120**, which proceeded in 88% yield and 93% ee (Scheme 2.24). Subsequent oxidation of the secondary alcohol to a ketone and protection of the tertiary alcohol as a TMS-ether furnished **2.123**.

Scheme 2.24 Synthesis of methyl ketone **2.123**

Unification of fragments **2.119** and **2.123** was achieved by an aldol condensation, which gave aldol adduct **2.124** as a mixture of diastereomers. Dehydration with the Burgess reagent gave unsaturated ketone **2.125**. The conjugated carbon-carbon double bond of **2.125** was selectively reduced using Stryker's reagent and the TMS protecting group was excised with TBAF to give **2.126**. Finally, removal of the TBS-ether protecting groups with HF formed an intermediate which cyclised spontaneously to furnish the hemiacetal of **2.127** in 49% yield.

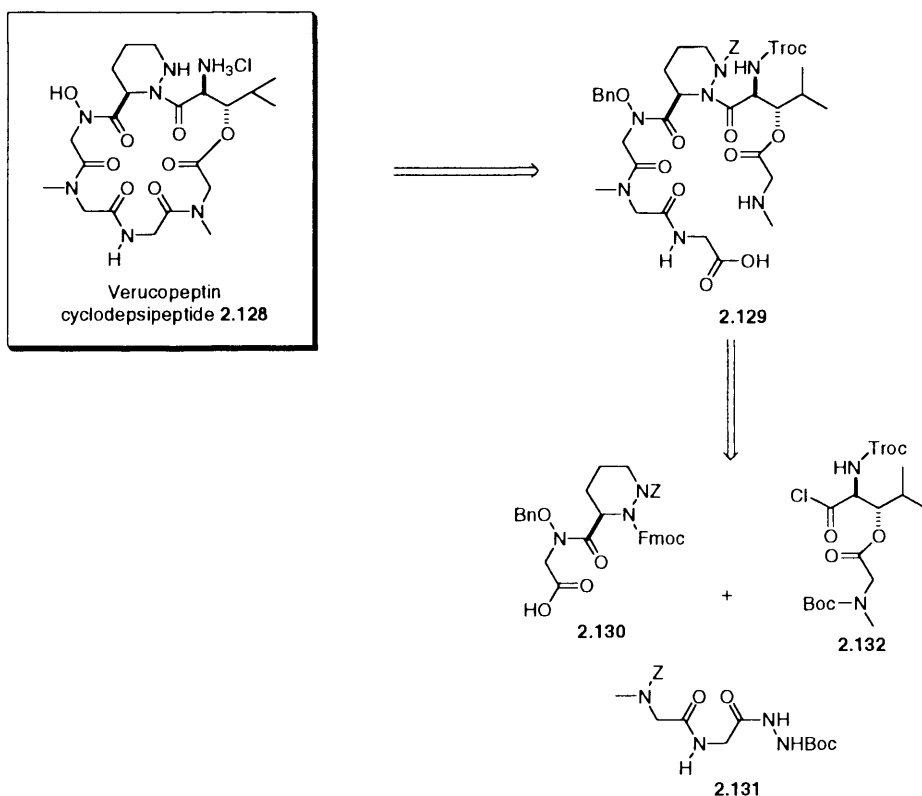




**Scheme 2.25** Synthesis of GE3 acyl side chain **2.127**

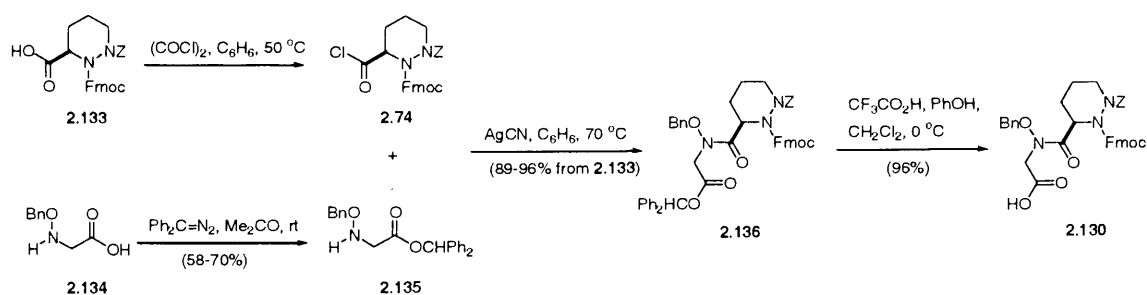
## 2.4 Synthetic studies towards verucopeptin

The relative and absolute stereochemistry of verucopeptin is at present unknown, meaning that there are 8 possible diastereomers of the verucopeptin cyclodepsipeptide core. Nevertheless, the fact that all other A83586C-azinothricin family members have a (3*R*)-piperazic acid unit linked to a (2*S*,3*S*)-3-hydroxyleucine suggests that an identical sequence exists in verucopeptin. As such, the Hale group adopted diastereomer **2.128** as their synthetic target<sup>50</sup> (Scheme 2.26). As in the syntheses of both A83586C and GE3, a [2+2+2] fragment condensation strategy involving was planned between dipeptides **2.130**, **2.131** and **2.132**. The resultant macrolactamisation precursor **2.129** could then be cyclised between its Gly and Sar termini without risk of epimerisation. Global deprotection would then yield cyclodepsipeptide **2.128**, which is primed for biomimetic coupling to appropriate activated ester pryan side chain structures.



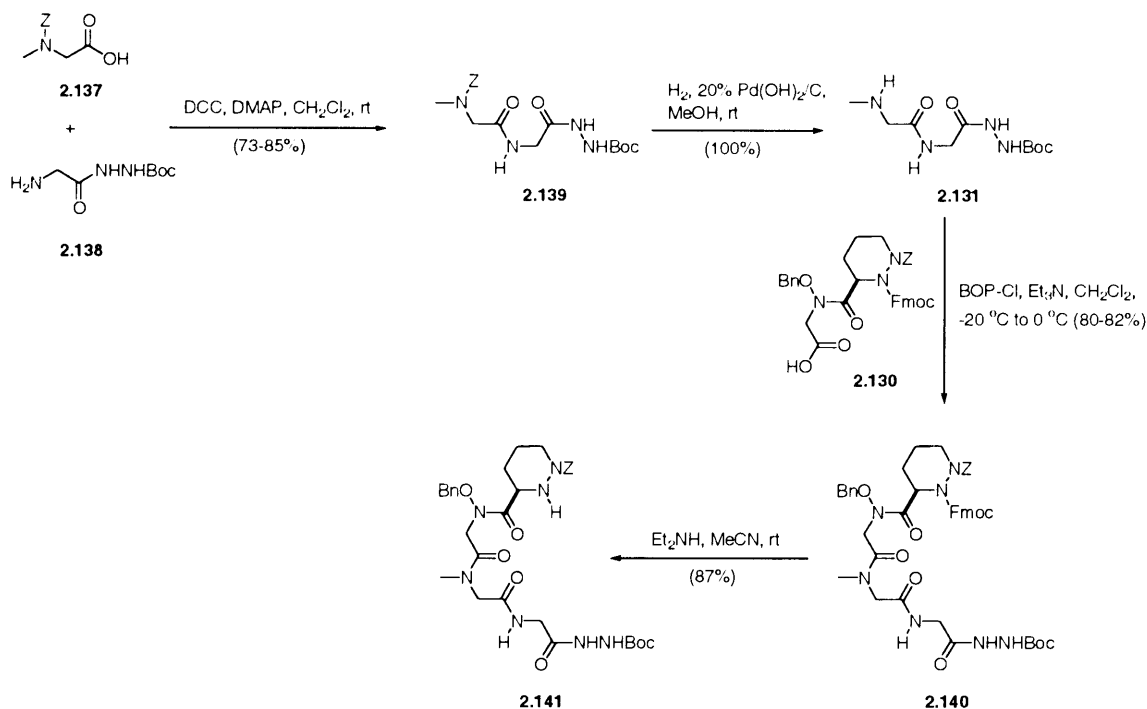
**Scheme 2.26** Hale's retrosynthetic analysis of the verucopeptin cyclodepsipeptide core

The Hale group's route to dipeptide **2.130** again required piperazic acid chloride **2.74**, which was accessed as described earlier in the A83586C/GE3 syntheses. The carboxyl group of known protected hydroxamic acid **2.134** was temporarily masked as a diphenylmethyl ester, and the free NH was coupled to acid chloride **2.74** in a reaction mediated by AgCN (Scheme 2.27). The diphenylmethyl ester grouping was then cleaved from dipeptide **2.136** with TFA to give acid **2.130**.



**Scheme 2.27** Synthesis of dipeptide **2.130**

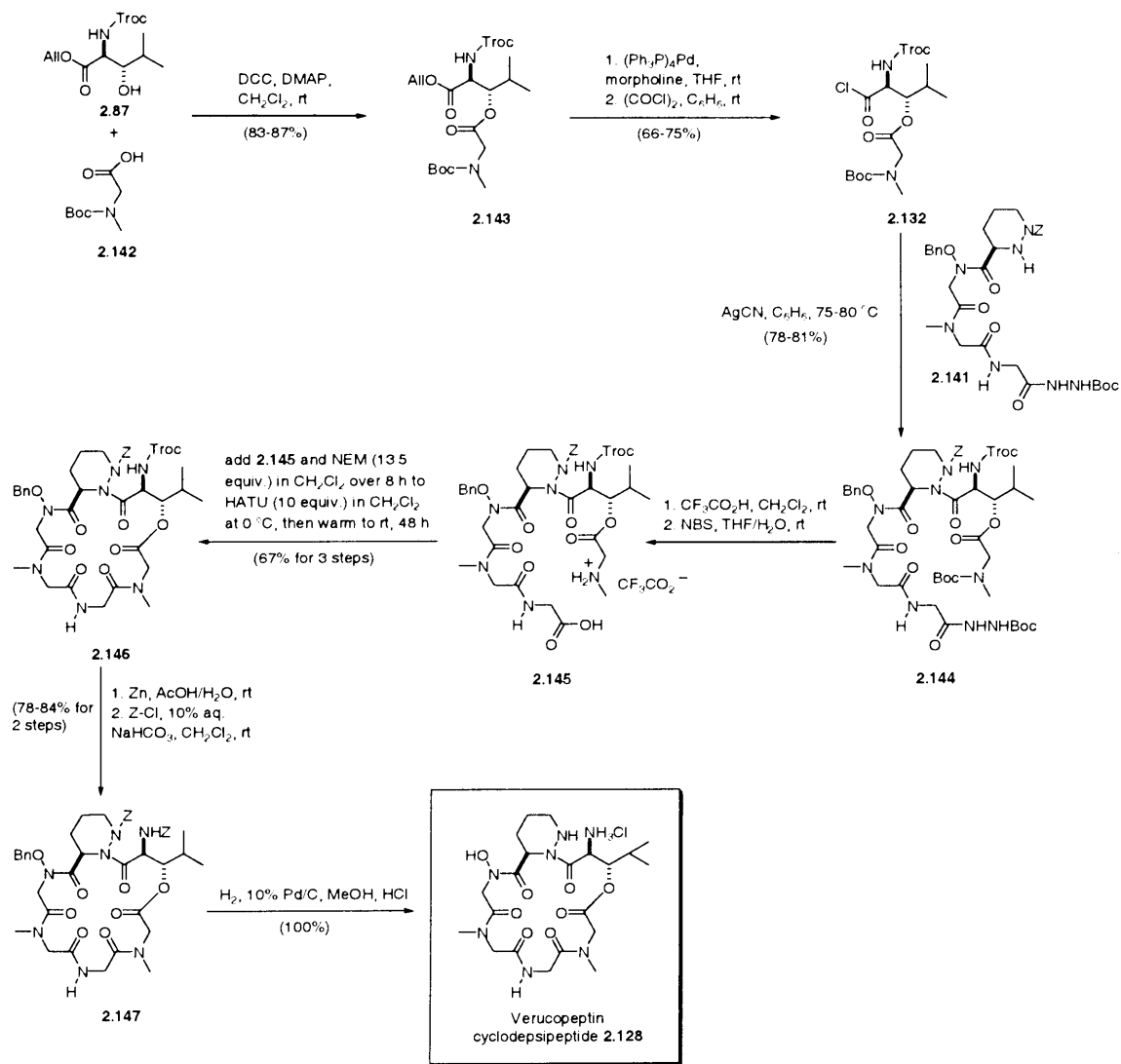
Dipeptide **2.131** was synthesised by coupling **2.137** and **2.138** under standard DCC conditions and cleaving the Z group from **3.139** by catalytic hydrogenolysis (Scheme 2.28). The dipeptides **2.130** and **2.131** were then linked together under BOP-Cl/Et<sub>3</sub>N conditions<sup>51</sup> to give **2.140**. Deprotection of the Fmoc group with diethylamine in MeCN then furnished tetrapeptide **2.141**.



**Scheme 2.28** Synthesis of tetrapeptide **2.141**

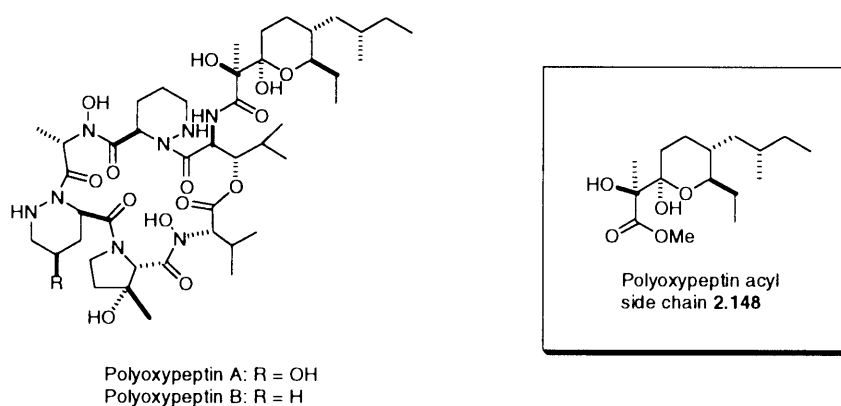
The next dipeptide fragment to be assembled was acid chloride **2.132**. It was formed by a DCC-DMAP promoted coupling between the known protected (2*S*,3*S*)-3-hydroxyleucine residue **2.87** and *N*-Boc Gly unit **2.142**, followed by deallylation with Pd(0)/morpholine<sup>52</sup> and a chlorination with oxalyl chloride in benzene (Scheme 2.29). Chemoselective *N*-acylation of tetrapeptide **2.141** with acid chloride **2.132** was achieved by heating to 80 °C with AgCN in benzene for no more than 2-3 minutes. The resultant hexapeptide **2.144** was treated with TFA to cleave the Boc groups, followed by NBS to convert the acyl hydrazine into the free acid **2.145**. This compound was primed for the key macrolactamization event, executed in high yield with Carpino's HATU reagent<sup>45</sup> to give **2.146**. The Troc group was detached from **2.146** with Zn dust in aqueous acetic acid, and the product amine was temporarily capped with a Z-

group to aid the final chromatographic purification of **2.147**. Removal of all the benzyl protecting groups by hydrogenolysis under mildly acidic conditions completed the Hale group's efficient synthetic route to the verucopeptin cyclodepsipeptide core structure.



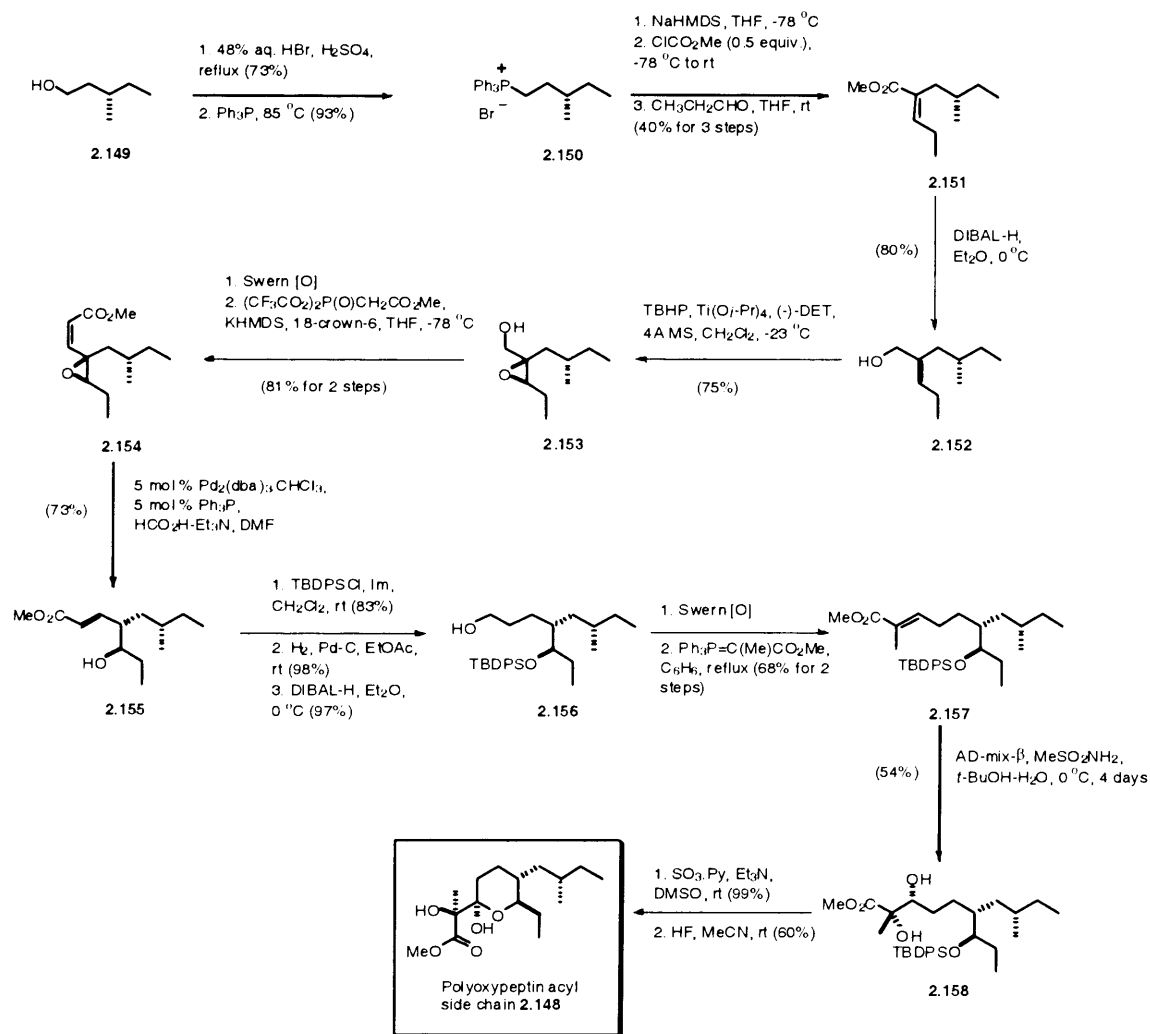
**Scheme 2.29** Synthesis of the verucopeptin cyclodepsipeptide

## 2.5 Synthetic studies towards Polyoxypeptins A and B



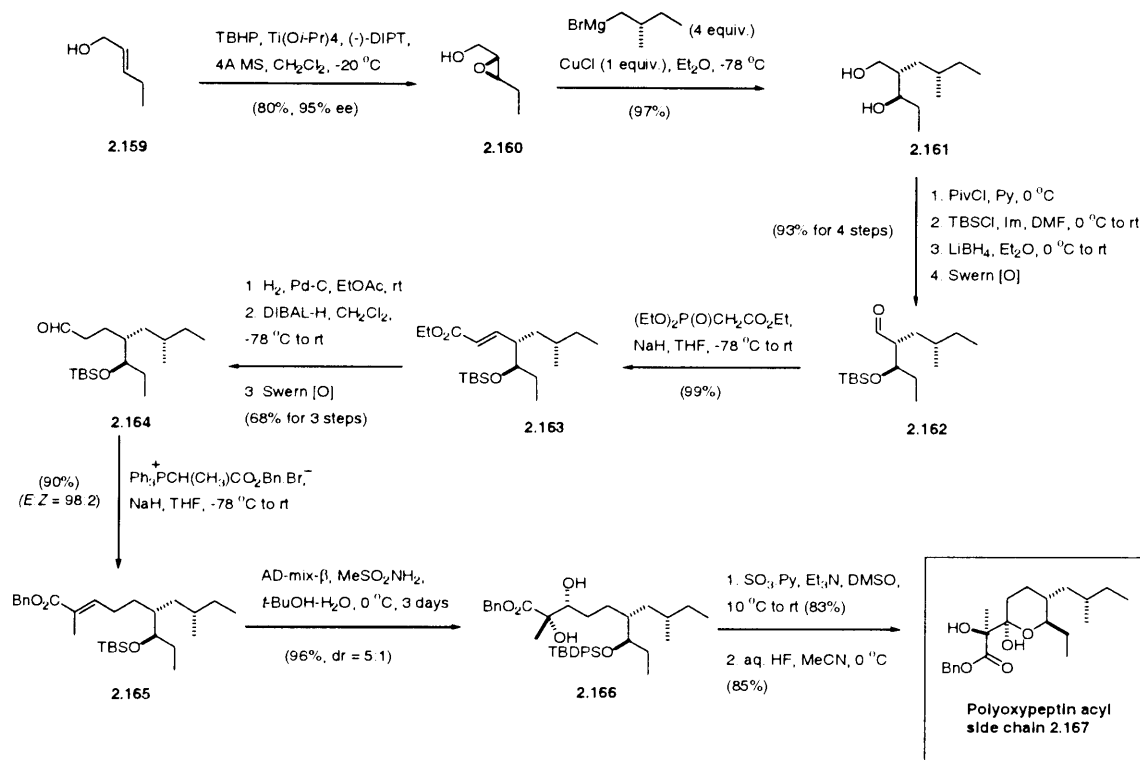
Scheme 2.30 Polyoxypeptins A and B

The polyoxypeptins (Scheme 2.30) have recently been the subject of intense efforts towards their total synthesis. Currently this remains elusive, although four syntheses of the acyl side chain have been published in the past few years. The first of these was reported by Kobayashi<sup>53</sup> in 2000 (Scheme 2.31). Chiral alcohol **2.149** (readily prepared from L-(+)-isoleucine) was transformed into allylic alcohol **2.152** in 6 steps, with a stereoselective Wittig reaction being used to set the (*E*)-double bond geometry. **2.152** was then subjected to a Sharpless asymmetric epoxidation reaction with D-(-)-tartrate to give epoxy-alcohol **2.153** as a single diastereomer. Swern oxidation and a (*Z*)-selective Wittig reaction gave **2.154**, which underwent stereospecific Pd-catalysed hydrogenolysis with Ph<sub>3</sub>P in DMF to furnish the desired *anti*-isomer **2.155**. This compound was converted into alkene **2.157** in five more steps, with another Wittig condensation being used to form the carbon-carbon double bond. Asymmetric dihydroxylation of this bond was then carried out with AD-mix-β to obtain diol **2.158**. Oxidation of the secondary hydroxyl group, followed by removal of the TBDPS-ether with HF-MeCN and concomitant hemiacetalization, completed the synthesis of the pyran side chain segment **2.148**.



**Scheme 2.31** Kobayashi's synthesis of the Polyoxypeptin acyl side chain

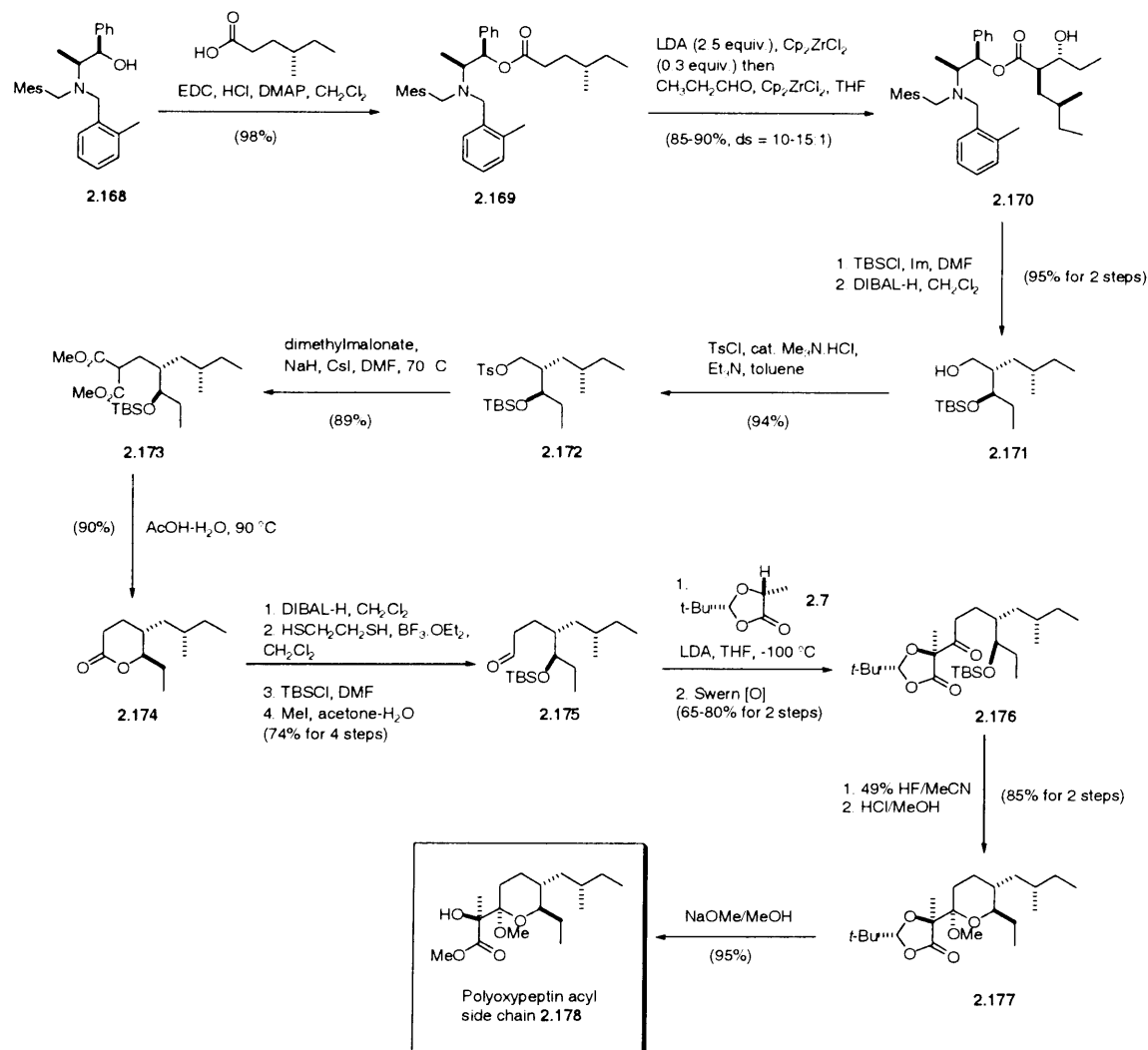
In 2002, Hamada<sup>54</sup> published a synthesis of the polyoxypeptin side chain which featured an endgame almost identical to Kobayashi's, with an asymmetric dihydroxylation of a Wittig adduct followed by oxidation and hemiacetalization steps (Scheme 2.32). However, the 1,2-*anti* stereochemistry of the side chain was introduced in a novel fashion. The key step was a regio- and stereoselective ring-opening of chiral 2,3-epoxy alcohol **2.160** (prepared via a Sharpless asymmetric epoxidation) by the Gilman reagent that was formed by combining (*S*)-2-methylbutylmagnesium bromide with CuCl in ether at -78 °C. The choice of the solvent and the counter ion in both the Grignard reagent and copper salt was found to be crucial in obtaining the desired regioselectivity to form the 1,3-diol **2.161**.



Scheme 2.32 Hamada's synthesis of the Polyoxypeptin acyl side chain

The polyoxypeptin side chain is very similar in structure to that of L-156,602, which was synthesised by Caldwell and Durette with an addition of Seebach's ester to a lactone being the key step (see Section 2.1). In 2001 the Kurosa group<sup>55</sup> attempted to apply this strategy to polyoxypeptin (Scheme 2.33). Their synthesis of the key intermediate lactone **2.174** commenced with a diastereoselective *anti*-aldol reaction of **2.169** with propionaldehyde to give aldol adduct **2.170** in high yield and 10-15:1 ds. The free hydroxyl was then protected as a TBS-ether, and the chiral auxiliary was reductively cleaved to give alcohol **2.171**. Tosylation of this compound was followed by substitution with malonate anion to furnish **2.173**. Treatment of the malonate adduct with 80%  $\text{AcOH}$  converted it into lactone **2.174** via the intermediate lactone-carboxylic acid. At this stage, the Kurosa group attempted to install the remaining three-carbon unit of their target by addition of the lithium enolate of the Seebach ester **2.7** to lactone **2.174**. However, in their hands, no addition was observed under the reaction conditions described by Seebach.<sup>27</sup> So, in order to facilitate a coupling reaction with **2.7**, lactone **2.174** was converted into aldehyde **2.175** via standard procedures. Addition of the lithium enolate of Seebach's ester **2.7** to aldehyde **2.175** occurred readily at  $-100$  to  $-95$

$^{\circ}\text{C}$  to give an alcohol that was oxidized to ketone **2.176** under Swern conditions. Treatment of **2.176** with HF in MeCN afforded a hemiketal, which was transformed into mixed methyl ketal **2.177** in HCl/MeOH. Transesterification with NaOMe in absolute MeOH then yielded the target polyoxypeptin acyl side chain **2.178**.

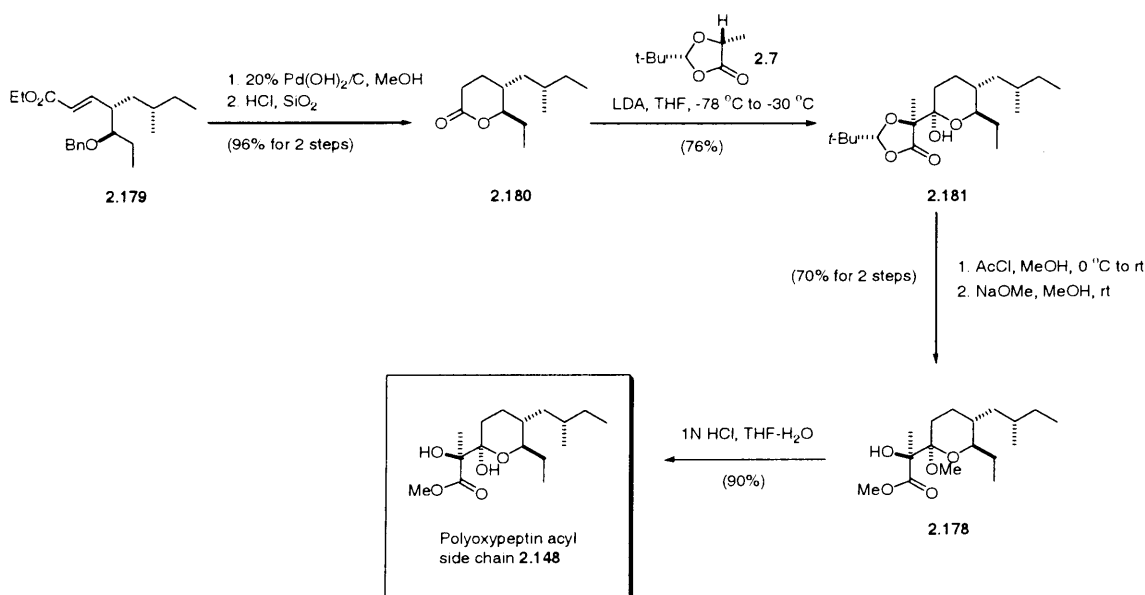


**Scheme 2.33** Kurosa's synthesis of the Polyoxypeptin acyl side chain

In 2002, Yao<sup>56</sup> was able to induce an aldol condensation to occur between a lactone and Seebach's ester (Scheme 2.34). The Yao group found that two equivalents of the lithium enolate of the Seebach ester **2.7** were required to force the addition to lactone **2.180** to give **2.181**. Also, it was necessary to raise the temperature from -78 to -30  $^{\circ}\text{C}$  to drive the reaction to completion. Fortunately, these reaction conditions did not lead to noticeable reduction in



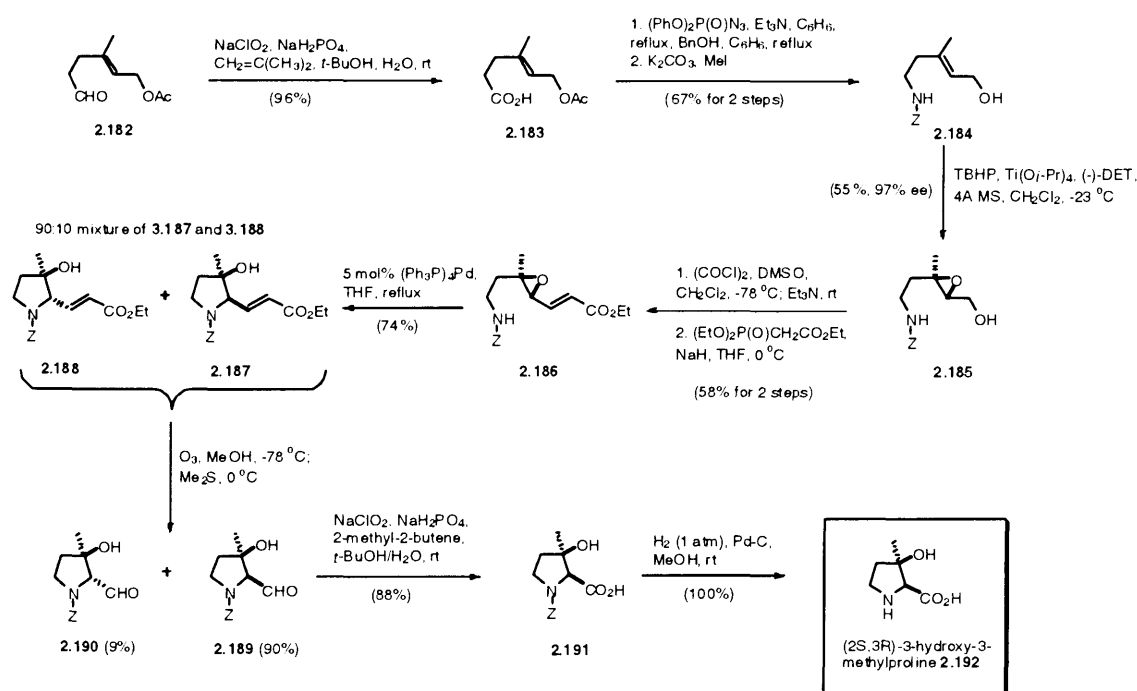
the diastereoselectivity of the transformation. Intermediate **2.179** was formed using the same strategy employed by Hamada and co-workers in their synthesis of the nearly identical intermediate **2.163**, i.e. with a stereo- and regioselective addition of an organocopper reagent to a chiral 2,3-epoxy alcohol as the key step. Hydrogenation of the carbon bond and hydrogenolysis of the benzyl group of **2.179** was carried out in one step, before acid-catalysed lactonization gave the key lactone **2.180**. Treatment of **2.181** with methanolic HCl accomplished smooth conversion into the methyl pyranoside intermediate, and subsequent transesterification of the resultant dioxalanone with an excess of sodium methoxide was used to remove the acetal protection and give **2.178**, a stable ester derivative that was previously synthesised by Kurosa. This could be converted into the diol derivative **2.148** with HCl in THF-water, a compound that allowed correlation with the Kobayashi synthetic route.



**Scheme 2.34** Yao's synthesis of the polyoxypeptin acyl side chain

Polyoxypeptin also contains two novel amino acid subunits, namely a (2*S*,3*S*)-3-hydroxy-3-methylproline and (3*S*,5*S*)-5-hydroxypiperazic acid, the latter being present only in polyoxypeptin A. Both of these residues have been the subject of several stereoselective syntheses. Kobayashi reported a synthesis of (2*S*,3*S*)-3-hydroxy-3-methylproline in 2001<sup>57</sup> (Scheme 2.35). The known aldehyde **2.182** (readily prepared from geraniol in 3 steps) was

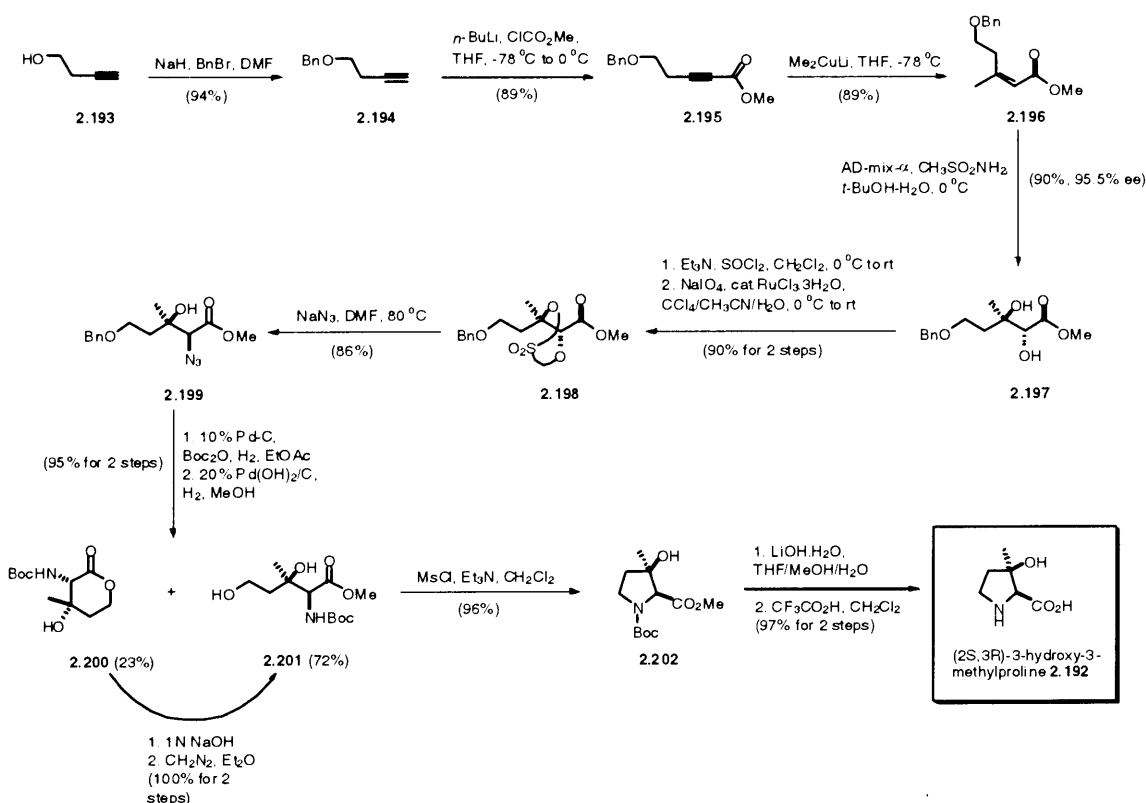
oxidized to carboxylic acid **2.183**, and the latter was subjected to a modified Curtius rearrangement using  $(\text{PhO})_2\text{P}(\text{O})\text{N}_3$  and benzyl alcohol, followed by deacetylation to afford an allylic alcohol **2.184**. Sharpless asymmetric epoxidation of this material gave chiral epoxyalcohol **2.185** with 97% ee. Swern oxidation and a Wittig olefination then furnished (*E*)-alkenyloxirane **2.186**, which was to be the substrate for the key Pd-catalysed cyclization. Accordingly, treatment of **2.186** with catalytic  $\text{Pd}(\text{PPh}_3)_4$  in THF under reflux gave a 90:10 mixture of pyrrolidine derivatives **2.187** and **2.188** in 74% combined yield via cyclization of a  $\pi$ -allyl palladium intermediate. Ozonolysis of this mixture gave the separable aldehyde **2.189** as the major product. Pinnick oxidation and finally hydrogenolysis of the Z protecting group completed Kobayashi's route to (*2S,3R*)-3-hydroxy-3-methylproline **2.192**.



**Scheme 2.35** Kobayashi's synthesis of (*2S,3R*)-3-hydroxy-3-methylproline

An alternative approach to (*2S,3R*)-3-hydroxy-3-methylproline was reported by Yao in 2002.<sup>58</sup> The synthesis commenced with preparation of acetylene **2.195** from commercially available 3-butyne-1-ol **2.193** in 2 steps (Scheme 2.36). Addition of acetylene **2.195** to  $\text{Me}_2\text{CuLi}$  in THF at  $-78^\circ\text{C}$  afforded the *Z*-olefin **2.196**, which was subjected to a Sharpless asymmetric dihydroxylation reaction to give diol **2.197** in 95% ee. Cyclic sulfate **2.198** was synthesised in

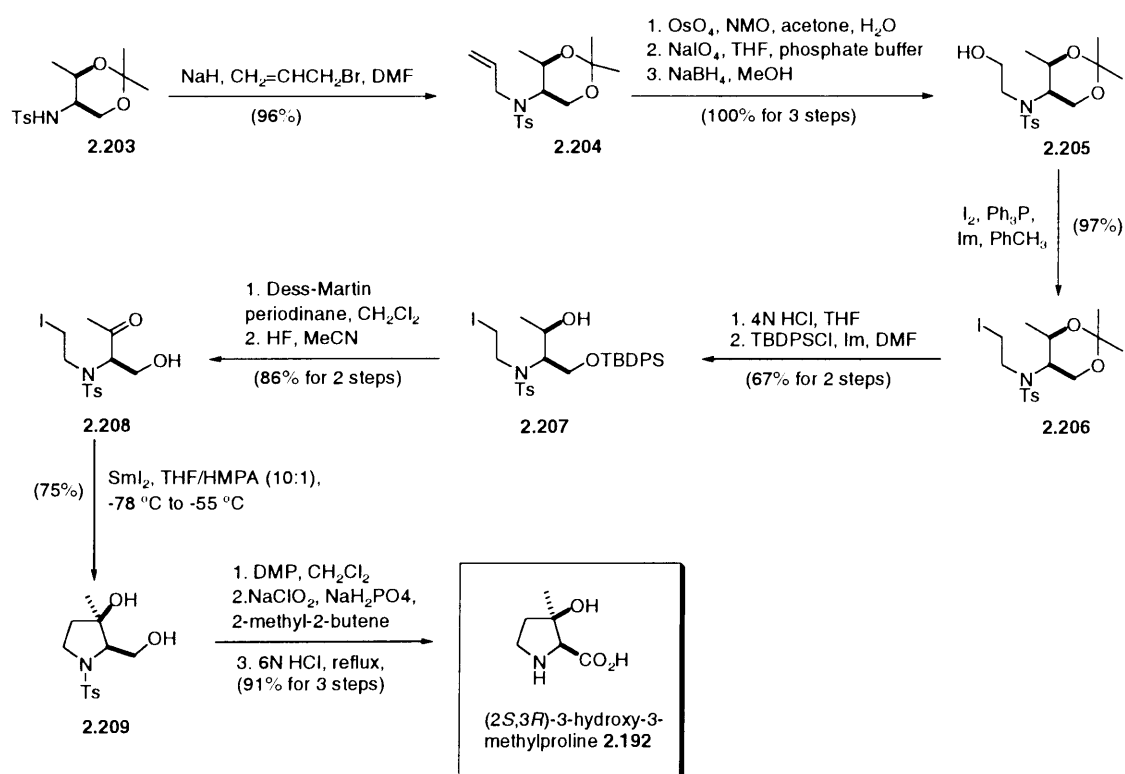
2 steps and then ring-opened regioselectively with  $\text{NaN}_3$ . The resultant azide **2.199** was reduced to diol **2.201**, with the by-product lactone **2.200** able to be converted into **2.201** quantitatively by alkaline hydrolysis. An intramolecular ring-closing reaction of diol **2.201** was then mediated by  $\text{MsCl}$  and  $\text{Et}_3\text{N}$  in  $\text{CH}_2\text{Cl}_2$  to give the desired pyrrolidine **2.202**. Finally the remaining protecting groups of **2.202** were removed by a two-step procedure with  $\text{LiOH}$  and  $\text{TFA}$  to furnish the targeted (2*S*,3*R*)-3-hydroxy-3-methylproline.



**Scheme 2.36** Yao's synthesis of (2*S*,3*R*)-3-hydroxy-3-methylproline

A third route to (2*S*,3*R*)-3-hydroxy-3-methylproline was also published in 2002 by the Hamada group<sup>59</sup> (Scheme 2.37). Their synthesis commenced with preparation of tosylamide **2.203** from (2*S*,3*R*)-threonine in 4 steps. *N*-Allylation of **2.203** gave alkene **2.204**, which was converted into primary alcohol **2.205** in 3 simple steps. Halogenation of the primary hydroxyl group of **2.205** with iodine and  $\text{Ph}_3\text{P}$  in the presence of imidazole provided iodoalkane **2.206**. After acid-catalysed deprotection of the isopropylidene acetal of **2.206**, the selective protection of the primary alcohol gave TBDPS-ether **2.207**. Subsequent oxidation of the

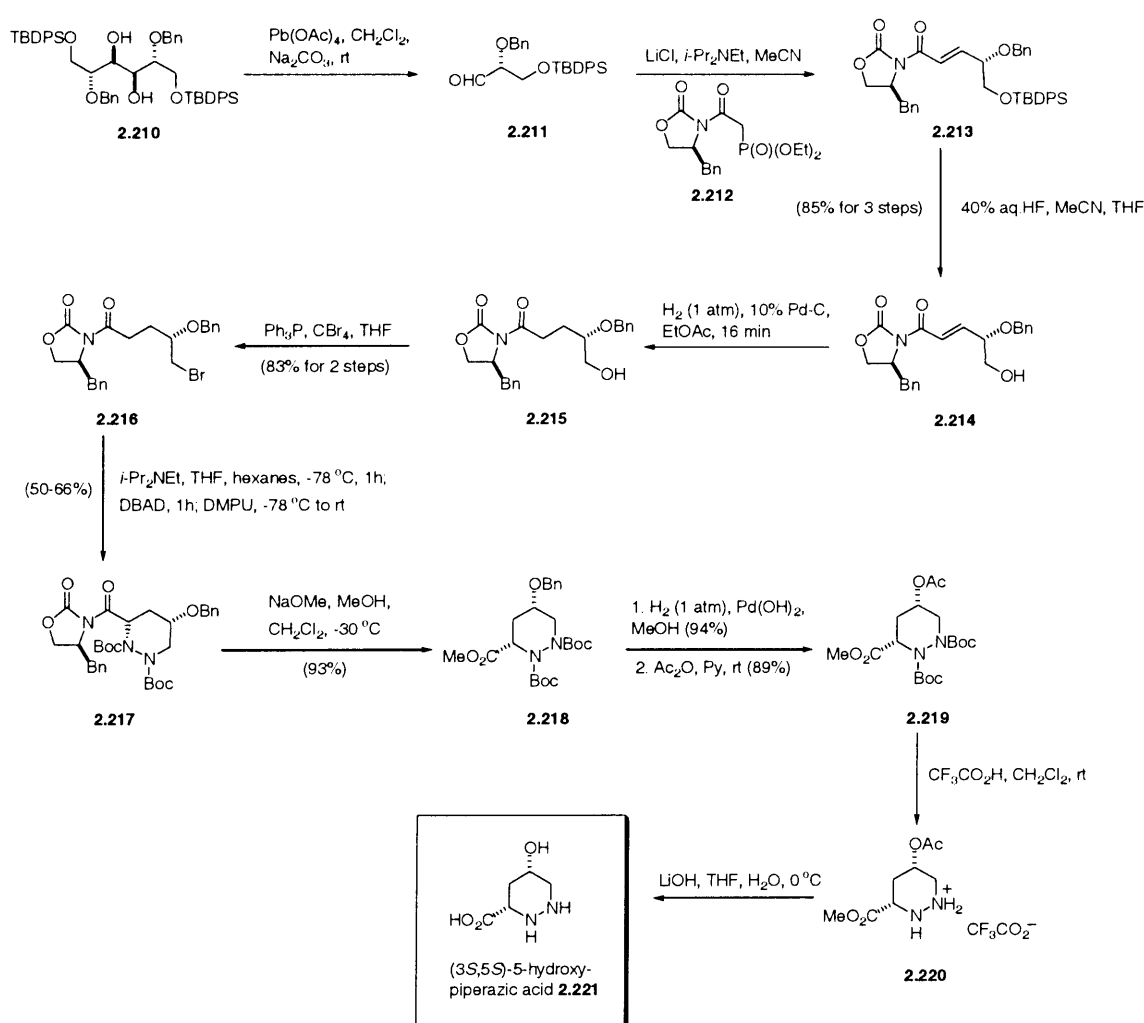
secondary alcohol using Dess-Martin periodinane and removal of the silyl protecting group furnished iodoketone **2.208**. This molecule was set up for the key step of Hamada's synthesis, a  $\text{SmI}_2$ -mediated cyclization. This reaction was carried out at  $-78$  to  $-55$  °C in THF/HMPA to yield **2.209** with high diastereoselectivity. The synthesis of (2*S*,3*R*)-3-hydroxy-3-methylproline **2.192** was completed by selective oxidation of the primary hydroxyl of **2.209** to a carboxyl group by application of stepwise Dess-Martin and Pinnick oxidations, and subsequent deprotection of the tosyl group with 6*N* HCl under refluxing conditions.



**Scheme 2.37** Hamada's synthesis of (2*S*,3*R*)-3-hydroxy-3-methylproline

The novel amino acid residue (3*S*,5*S*)-5-hydroxypiperazic acid **2.220** was first synthesised in an enantiocontrolled manner by the Hale group in 1998.<sup>60</sup> The starting material for their route was *D*-mannitol derivative **2.210** (Scheme 2.38). Oxidative cleavage of this compound with  $\text{Pb}(\text{OAc})_4$  gave aldehyde **2.211** which readily participated in a Horner-Wittig olefination with known phosphonate **2.212** under the Roush-Masamune conditions. This produced the crystalline alkene **2.213** as the (*Z*)-isomer. Cleavage of the TBDPS-ether with 40% aq. HF in THF/MeCN then gave alcohol **2.214**. Chemoselective hydrogenation of the olefin double bond

furnished alcohol **2.215** without removal of the *O*-benzyl group. Bromide **2.216** was then formed by bromination with  $\text{CBr}_4$  and  $\text{PPh}_3$ . This compound was primed for the key step in Hale's synthesis, namely a stereoselective hydrazination with di-*tert*-butylazodicarboxylate and tandem nucleophilic cyclization of the resultant aza anion. This gave the cyclized product **2.217** in 50-66% yield after chromatographic purification. Cleavage of the chiral auxiliary was then accomplished by treating **2.217** with  $\text{NaOMe}$  in  $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , furnishing the methyl ester **2.218**.

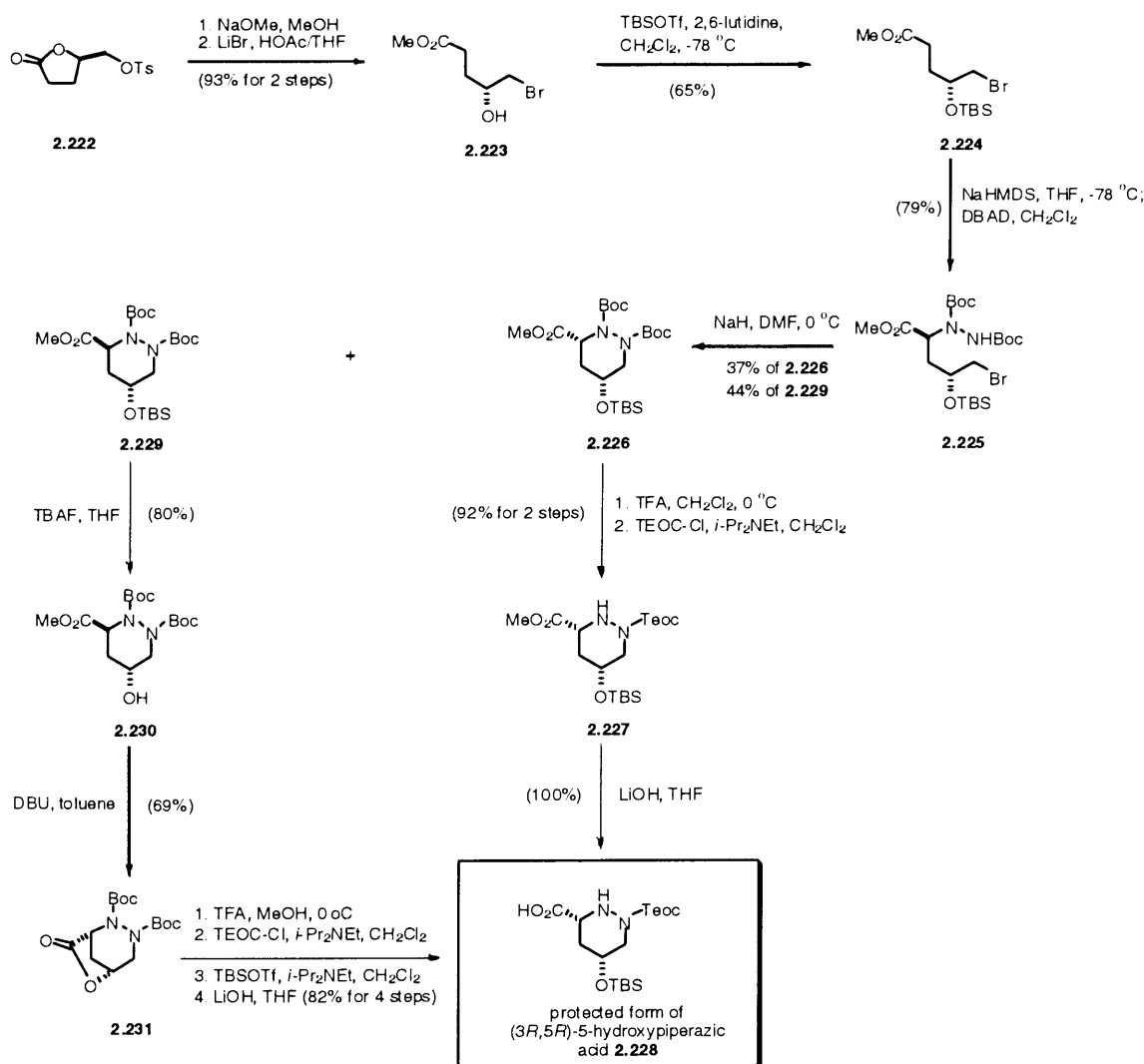


**Scheme 2.38** Hale's synthesis of (3*S*,5*S*)-5-hydroxypiperazic acid

The *O*-benzyl group was then cleaved by catalytic hydrogenolysis with  $\text{Pd}(\text{OH})_2$  in MeOH, and the resulting alcohol temporarily *O*-acetylated to obtain **2.219**. This permitted a clean and high yielding deprotection of the two Boc groups with TFA. Crude **2.220** was then reacted with

LiOH in THF-water to obtain (3*S*,5*S*)-5-hydroxypiperazic acid **2.221**. Importantly, this route could be applied to the preparation of partially protected (3*S*,5*S*)-5-hydroxypiperazic acid derivatives useful for further synthetic work.

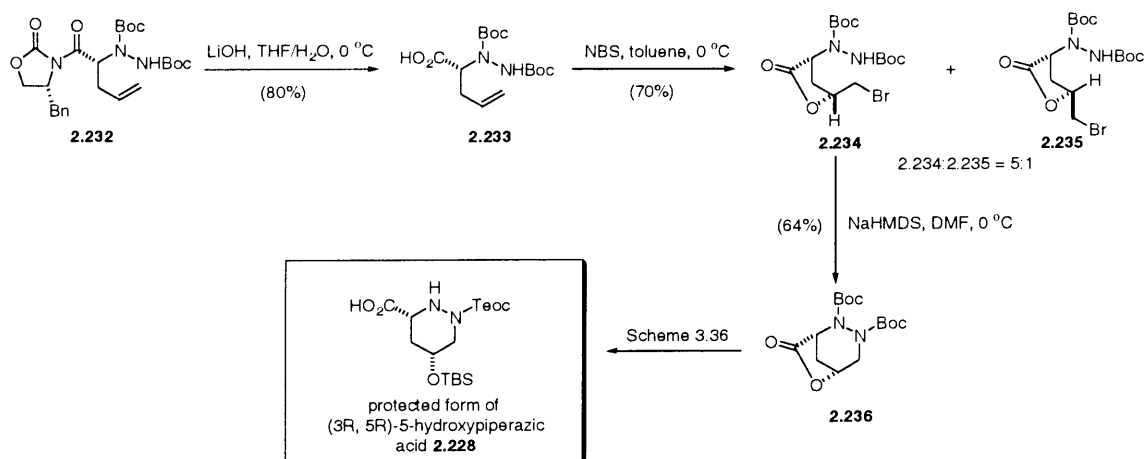
A (3*R*,5*R*)-5-hydroxypiperazic acid derivative is present in the dimeric cyclodepsipeptide himastatin. As part of the Danishefsky group's studies towards the total synthesis of this compound, two routes to protected forms of (3*R*,5*R*)-5-hydroxypiperazic acid were devised.<sup>61</sup> The first of these used D-glutamic acid as the starting material, which was converted into lactone **2.222** in three steps (scheme 2.39).



**Scheme 2.39** Danishefsky's first synthesis of protected (3*R*,5*R*)-5-hydroxypiperazic acid

Advancement of **2.222** to the known epoxy ester was followed by ring-opening with LiBr and AcOH to provide hydroxy ester **2.223**. Protection of the secondary alcohol as its TBS-ether afforded **2.224**, which was aminated with di-*tert*-butyl azodicarboxylate to give **2.225** as a 1:1 mixture of diastereomers. Treatment of this material with NaH in DMF induced cyclization to give piperazic esters **2.226** and **2.229**. Removal of the Boc groups from the *cis* ester **2.226** and selective protection of the more reactive N1 nitrogen with a Teoc group amino ester **2.227**. Conversion to piperazic acid **2.228** was accomplished by facile hydrolysis with LiOH. The *trans* ester **2.229** could also be converted to **2.228** via alcohol **2.230** and the *cis* piperazic lactone **2.231**.

The second stereoselective route to a protected form of (3*R*,5*R*)-5-hydroxypiperazic acid developed by the Danishefsky group utilizes an Evans asymmetric amination to give **2.232** (Scheme 2.40). Cleavage of the auxiliary acyloxazolidinone bond with LiOH in THF-water gave acid **2.233**, which underwent a diastereoselective bromolactonization to furnish a separable 5:1 mixture of the desired *cis* lactone **2.234** and the undesired *trans* lactone **2.235**. Deprotonation of the N1 nitrogen of **2.234** caused displacement of bromide and concomitant cyclization to **2.236**, which could be converted into **2.228** as described in Scheme 2.39.



**Scheme 2.40** Danishefsky's second synthesis of protected (3*R*,5*R*)-5-hydroxypiperazic acid

## Chapter 3 Results and Discussion

The ultimate goal of our synthetic work on the azinotricin family of cyclodepsipeptide molecules was to make significant quantities of the natural products and designed analogues. These molecules could then serve as valuable probes of physiological systems due to their high biological activity. In order to do this, a highly efficient and scalable second-generation synthesis of the acyl pyran side chain was required. We felt that the first-generation synthesis described in Chapter 2 could be considerably improved, as some steps of the original route exhibited poor stereo- or regioselectivity. A reduction in the total number of steps would also be of considerable benefit in terms of material throughput to the coupled natural product structures. Ideally, a new route would be flexible enough to incorporate well-designed modifications of the side chain during analogue construction.

### 3.1 A second generation total synthesis of the acyl side chain of A83586C

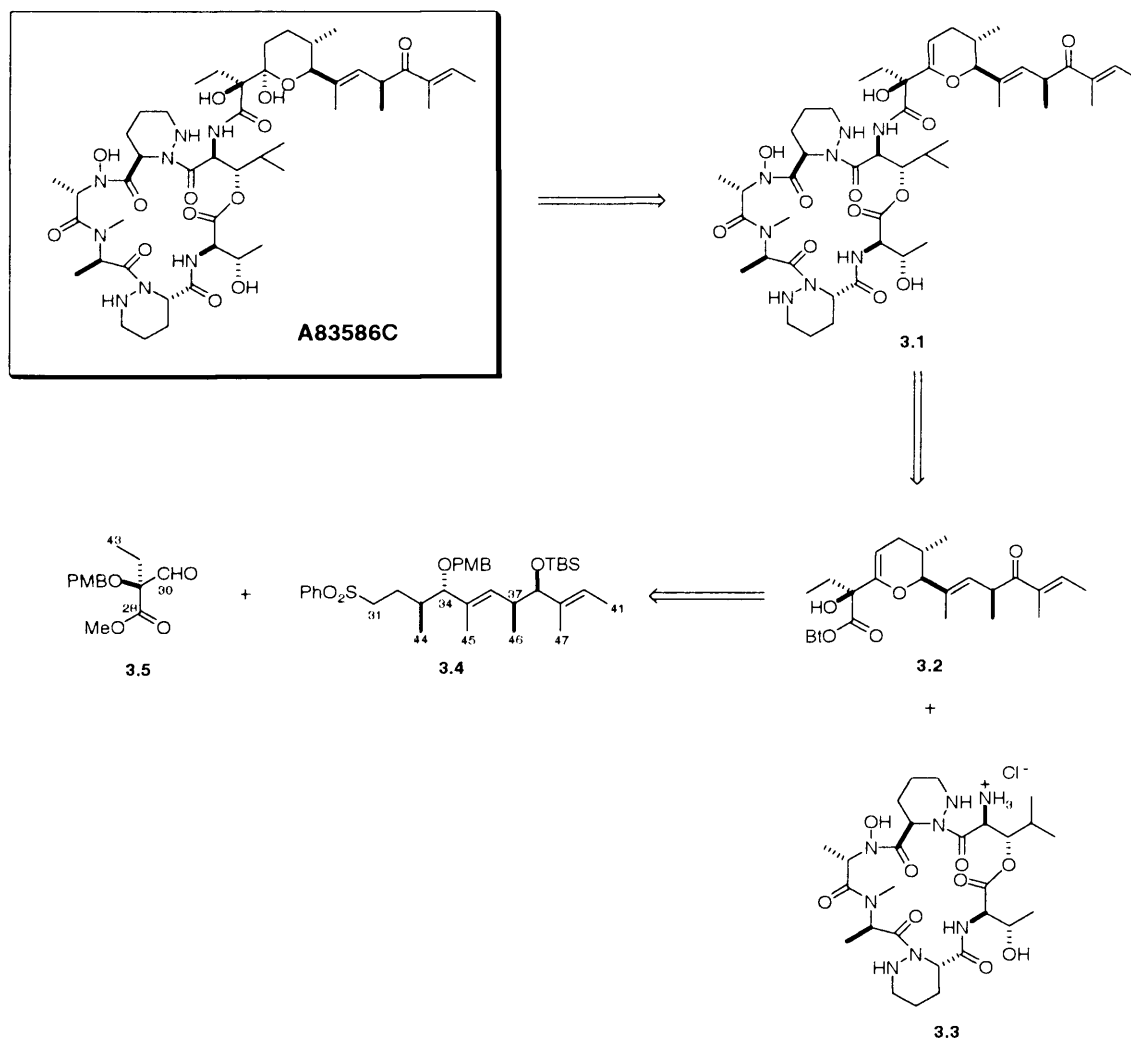
#### 3.1.1 Retrosynthetic analysis of A83586C

In the course of these second-generation studies, it was deemed prudent not to alter the basics of the endgame strategy (Scheme 3.1). Indeed, it is hard to envisage how the final coupling between a fully deprotected cyclodepsipeptide such as **3.2** and a similarly deprotected activated ester **3.3** could be conducted in any other way, since any oxidation, reduction or deprotection steps that might be required after a unification event would be very hard to achieve, owing to the highly sensitive nature of the coupled structures. The final step would again be the chemo- and stereoselective hydration of glycal **3.1**.

Given that the coupling between sulfone **3.4** and aldehyde **3.5** is a well-established and robust process, as is the subsequent ring closure to form the glycal motif of **3.2**, we decided to retain this sequence for construction of the C(30)-C(31) bond. Thus, we were able to focus mainly on new synthetic approaches to sulfone **3.4** and aldehyde **3.5**.



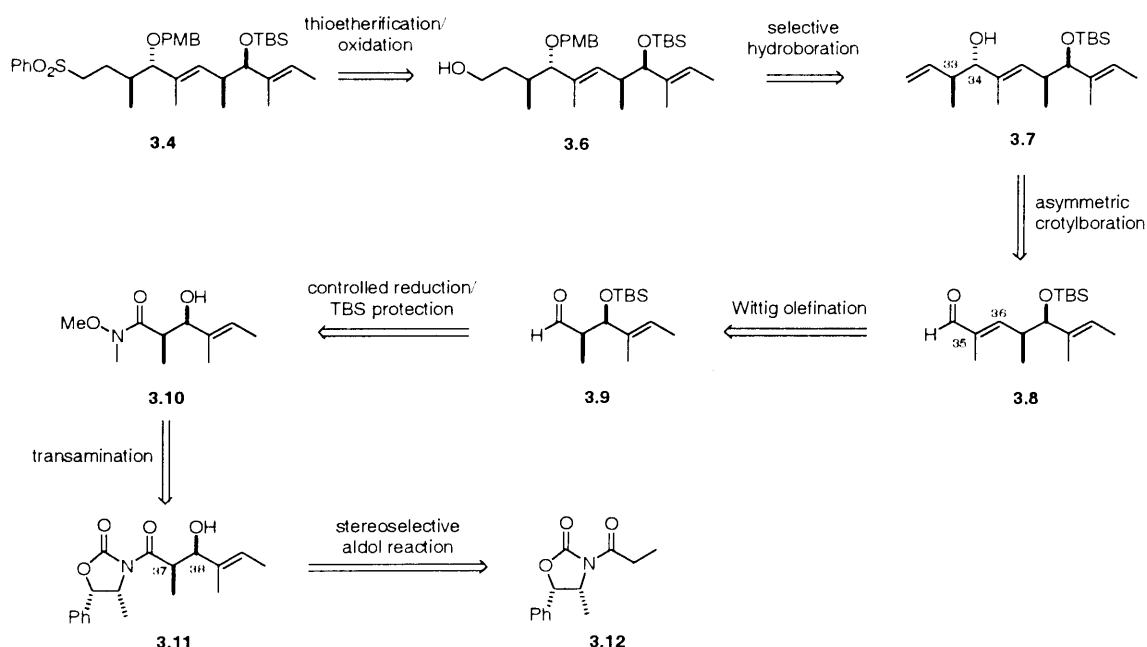
In this regard, practical syntheses of phenylsulfone **3.4** and aldehyde **3.5** were developed, as described in this section. Several other possible synthetic approaches to sulfone **3.4** were also investigated and evaluated, and these are summarized in Section 3.2. Finally, the successful strategy was applied to the total synthesis of azinothricin, as reported in Section 3.3.



**Scheme 3.1** Retrosynthetic plan for the A83586C class of natural products

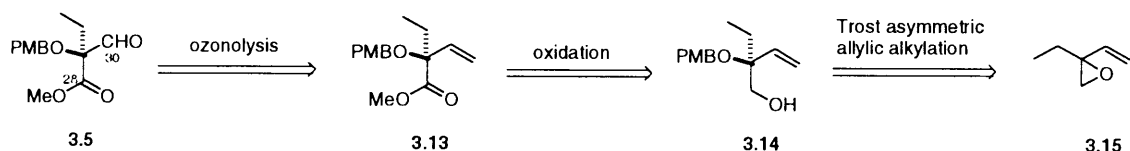
The successful second-generation strategy for the synthesis of the C(31)-C(47) sulfone fragment **3.4** is outlined in Scheme 3.2. It was envisaged that sulfone **3.4** could be derived from alcohol **3.6** via thioetherification and subsequent Trost-Curran<sup>62</sup> oxidation. Primary alcohol **3.6** would be obtainable from a regioselective hydroboration of terminal alkene **3.7**

using a carefully chosen borane reagent. An asymmetric crotylation of the  $\alpha,\beta$ -unsaturated aldehyde **3.8** could conveniently be used to construct both the C(33) and C(34) stereocentres of alkene **3.7**. The (*E*)-geometry of the C(35)-C(36) double bond could be installed by a Wittig reaction between aldehyde **3.6** and a suitably stabilised phosphonium ylide. Aldehyde **3.9** could in turn be derived from a controlled reduction of Weinreb amide<sup>63</sup> **3.10**, which could be formed from the transamination of **3.11**. This is the expected product of a fully stereocontrolled Evans aldol reaction<sup>64</sup> between *N*-propionyl oxazolidinone **3.12** and tiglic aldehyde, the *syn*-aldol reaction setting both the C(37) and C(38) chiral centres and the C(39)-C(40) double bond in a single step.



### Scheme 3.2 Retrosynthetic analysis of sulfone **3.4**

Our retrosynthetic analysis of the simpler aldehyde C(28)-C(30) fragment **3.5** envisaged that it could be accessed from a stable terminal alkene precursor **3.13** by ozonolysis or oxidative cleavage of the carbon-carbon double bond (Scheme 3.3). Alteration of the oxidation state at C(28) suggests alcohol **3.14** as an intermediate, which could be formed from the racemic vinyl epoxide **3.15** via a Pd-catalysed asymmetric allylic alkylation reaction of the type pioneered by Trost.<sup>65,66</sup>

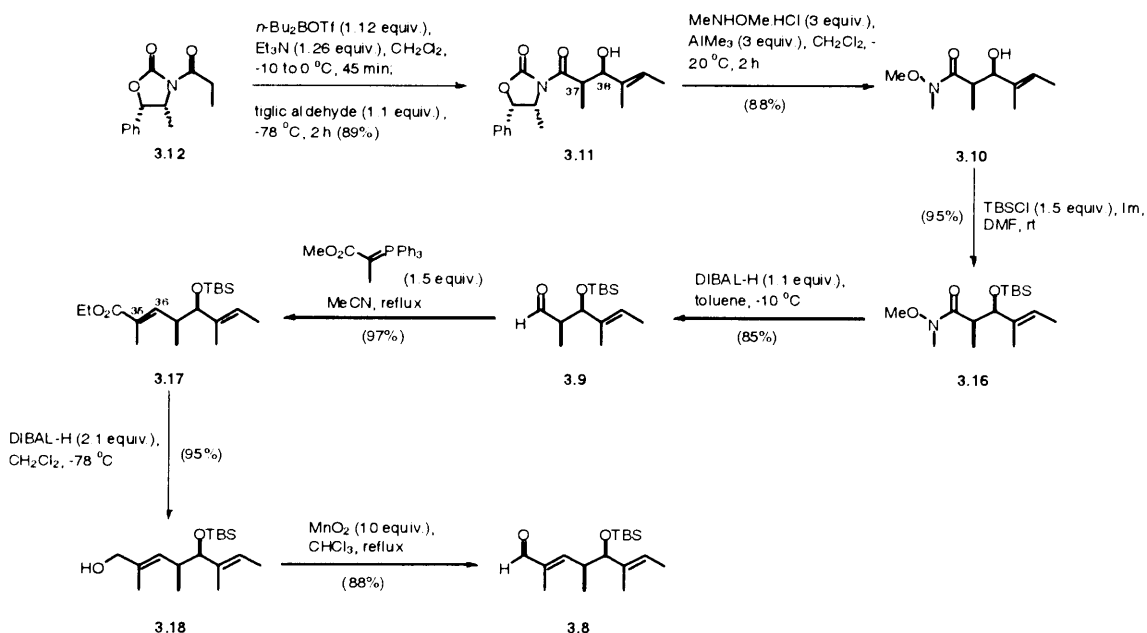


**Scheme 3.3** Retrosynthetic analysis of aldehyde **3.5**

### 3.1.2 Synthesis of the Acyl Side Chain of A83586C

The first step of the route to the C(31)-C(47) sulfone fragment **3.4** was therefore an Evans' *syn*-aldol reaction<sup>64</sup> between the boron enolate derived from *N*-propionyl-2-oxazolidinone **3.12** and tiglic aldehyde (Scheme 3.4). In this procedure, the (*Z*)-enolate was formed by careful reaction of **3.12** with triethylamine and di-*n*-butylboron triflate at -10 °C in CH<sub>2</sub>Cl<sub>2</sub>. Slow addition of tiglic aldehyde at -78 °C gave the *syn*-aldol adduct **3.11** in 85% yield as a single diastereoisomer, thus setting both the C(37) and C(38) stereocentres in one step. Compound **3.11** was identical in spectra and  $[\alpha]_D$  to **2.48** (page 28), and was obtained as a white crystalline solid after crystallization from petrol/ether. Transamination of this imide to form Weinreb amide<sup>63</sup> **3.10** was achieved by treatment with AlMe<sub>3</sub> and MeNH(OMe).HCl, the reaction proceeding in 88% yield after flash chromatography. Alternatively, the material could be taken on crude after selective crystallization of the chiral oxazolidinone auxiliary from petrol/ether. The next step was protection of the secondary hydroxyl of **3.10** as a TBS-ether, accomplished by stirring the material with TBSCl and imidazole in DMF at room temperature. Weinreb amide **3.16** was then carefully reduced by DIBAL-H in anhydrous toluene at -10 °C to furnish aldehyde **3.9**. Under these conditions, the intermediate adduct formed by addition of one hydride equivalent to the carbonyl group is stabilized by chelation with the metal ion, and thus further reduction to the alcohol is avoided. The aldehyde was liberated from the chelate by quenching with Rochelle's salt solution, and the highly non-polar product **3.9** was purified by a rapid SiO<sub>2</sub> flash chromatography step. A Wittig reaction between aldehyde **3.9** and the stabilized phosphorus ylide (carbethoxyethylidene)triphenylphosphorane was then used to install the C(35)-C(36) (*E*)- double bond, with the  $\alpha,\beta$ -unsaturated ester **3.17** being formed in 97% yield after heating at reflux in MeCN for 36 h. Treatment of ester **3.17** with 2 equivalents

of DIBAL-H in  $\text{CH}_2\text{Cl}_2$  achieved reduction to the allylic alcohol **3.18**. This compound was taken on crude and oxidized with  $\text{MnO}_2$  in refluxing  $\text{CHCl}_3$  to give the  $\alpha,\beta$ -unsaturated aldehyde **3.8** in 84% yield for the two steps.



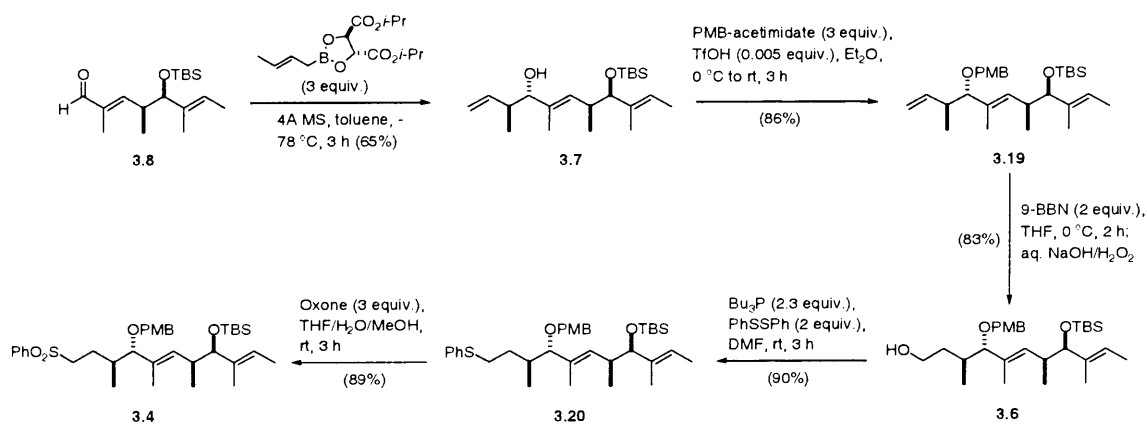
**Scheme 3.4** Synthesis of aldehyde **3.8**

In order to set the C(33)-C(34) *anti*-stereochemistry, aldehyde **3.8** was subjected to an asymmetric crotylboration with (*R,R*)-diisopropyl tartrate (*E*)-crotylboronate according to the procedure developed by Roush.<sup>67</sup> The crotylboronate was formed by metalation of *trans*-2-butene with *n*-BuLi/KOt-Bu followed by treatment of the (*E*)-crotylpotassium with (*i*-PrO)<sub>3</sub>B, aqueous hydrolysis, and esterification with diisopropyl tartrate. The resultant crotylboronate was stirred with aldehyde **3.8** for 3 h at  $-78^\circ\text{C}$  in anhydrous toluene, forming allylic alcohol **3.7** as a 2.3:1 mixture of diastereomers (Scheme 3.5). The desired isomer was separated from the undesired by careful flash chromatography on silica gel with 100:1 petrol-EtOAc as the eluent. The reaction cleanly went to completion and could be carried out on a large scale, so despite the relatively low stereoselectivity an acceptable yield of 65% of **3.7** could be obtained. Application of Brown's asymmetric crotylboration protocol<sup>68</sup> with (*E*)-crotyldiisopinocampheyl-borane gave inferior stereoselectivity, which is perhaps unsurprising

given that the reaction of unsaturated aldehydes with such chiral boronates is generally known to provide homoallylic alcohols in low to moderate stereoselectivity.

The next step was protection of the free secondary alcohol of **3.7** as a PMB-ether with PMB-acetimidate and catalytic TfOH in ether at 0 °C. The resultant triene **3.19** was smoothly converted into alcohol **3.6** in 83% yield via a highly regio- and stereoselective hydroboration reaction with 9-BBN in THF at 0 °C followed by oxidation with alkaline hydrogen peroxide. Several other hydroboration reaction conditions were examined, such as dicyclohexylborane and catecholborane with catalytic Wilkinson's catalyst, but they gave inferior yields. Presumably it is the steric bulk of 9-BBN that allows a selective hydroboration of such a multiply unsaturated substrate to occur.

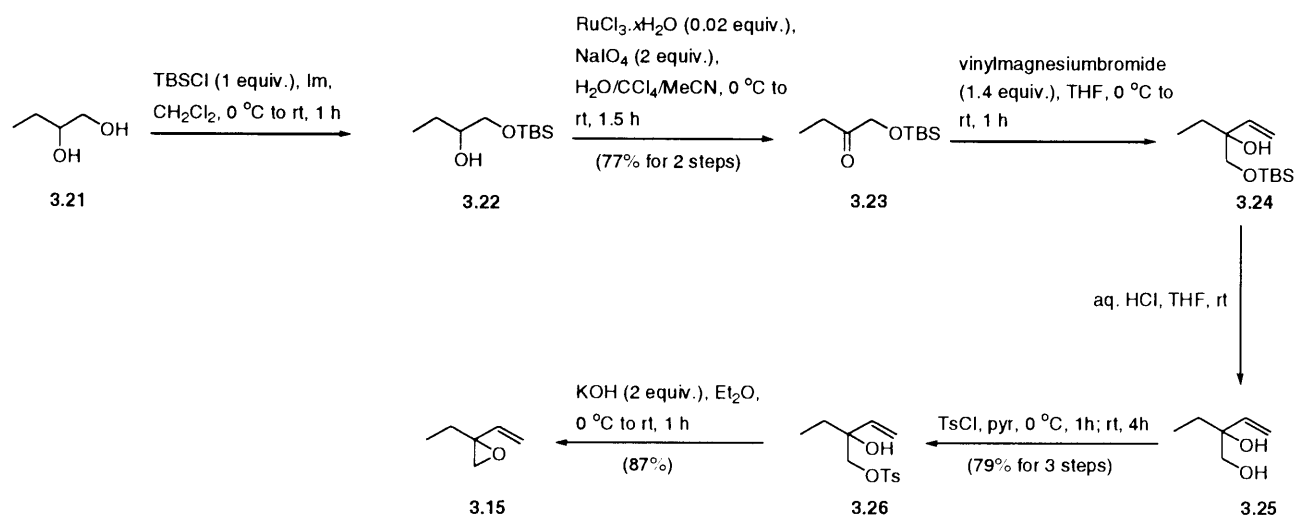
Thioetherification of alcohol **3.6** with tri-*n*-butylphosphine and diphenyl disulfide in DMF at room temperature then gave phenyl sulfide **3.20** in 90% yield. This compound was oxidized to phenylsulfone **3.4** with Oxone<sup>TM</sup> in THF/MeOH/H<sub>2</sub>O. TLC analysis of this reaction showed initial formation of a transient sulfoxide species, which was gradually converted into **3.4** over 3 h at room temperature. This completed the route to the key sulfone **3.4** in overall yield of 19% for the 12 steps from **3.12**. The synthetic scheme was highly robust and adaptable to large scale, and over 20 g of the sulfone was prepared in this way.



**Scheme 3.5** Synthesis of phenyl sulfone **3.4**

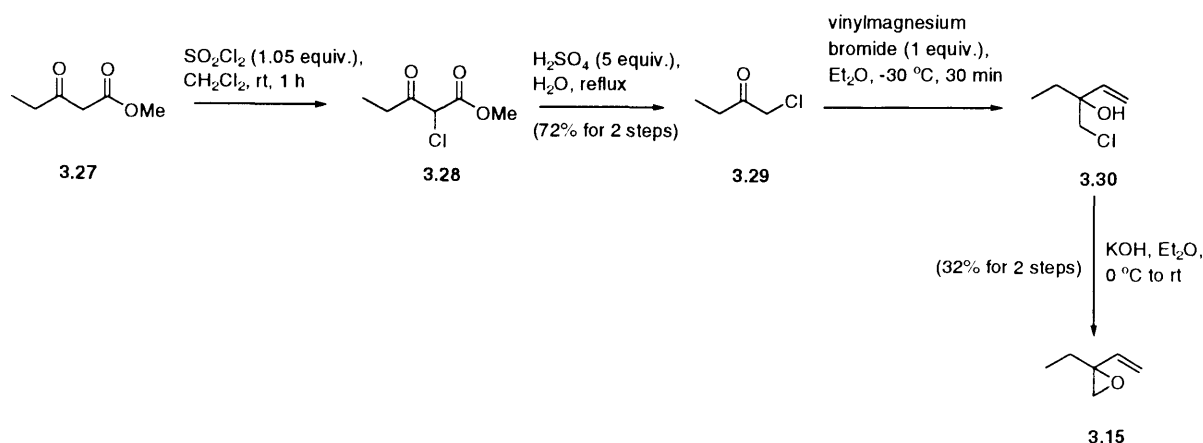
In order to correlate with a previous synthesis of the TBDPS analogue of sulfone **3.4**, the above route was repeated with a TBDPS group being attached to Weinreb amide **3.10** instead of a TBS group early in the synthesis. The obtained TBDPS protected sulfone was gratifyingly found to be identical to that previously made, thus validating the stereochemistry assigned to sulfone **3.4**. We later converted sulfone **3.4** into compound **3.39**, an advanced intermediate in our first generation route; the compound prepared by the new route was identical according to the 500 MHz  $^1\text{H}$  NMR spectrum in  $\text{CDCl}_3$  (see Scheme 3.11).

A key intermediate in the synthesis of aldehyde **3.5** was the chiral racemic vinyl epoxide **3.15**. This compound was synthesised on a large scale by two routes, the first of which employed 1,2-butanediol **3.21** as the starting material (Scheme 3.6). Chemoselective protection of the primary hydroxyl as a TBS-ether was accomplished by treatment with TBSCl and imidazole in  $\text{CH}_2\text{Cl}_2$  according to a known procedure.<sup>34</sup> The product **3.22** was taken on crude and oxidized with catalytic  $\text{RuCl}_3$  and  $\text{NaIO}_4$  in  $\text{MeCN}/\text{CCl}_4/\text{H}_2\text{O}$  to give ketone **3.23** in 77% yield for the two steps after a rapid chromatographic purification through a short pad of silica gel. Addition of vinylmagnesium bromide to **3.23** furnished the vinyl alcohol **3.24**. Cleavage of the TBS group gave diol **3.25**, which was subjected to a chemoselective mono-tosylation with  $\text{TsCl}$  in pyridine/ $\text{CH}_2\text{Cl}_2$  to give **3.26** in 79% yield over 3 steps after another chromatographic purification. The tosylate **3.26** was then treated with 2 equiv. of ground  $\text{KOH}$  in  $\text{Et}_2\text{O}$  at  $0^\circ\text{C}$  to accomplish an intramolecular  $\text{S}_{\text{N}}2$  cyclization reaction to give the volatile vinyl epoxide **3.15** in 87% yield after purification by fractional distillation. Formation of the vinyl epoxide was confirmed by  $^1\text{H}$  NMR spectroscopy, which showed distinctive doublets at 2.79 and 2.65 ppm corresponding to the  $\text{CH}_2$  protons of the oxirane ring. Overall this route to epoxide **3.15** was highly efficient, proceeding in 53% yield for six steps and requiring only two flash chromatography purification procedures. A single batch of over 20 g of **3.15** was prepared by this route.



**Scheme 3.6** Synthesis of epoxide **3.15** from 1,2-butanediol **3.21**

An alternative, and slightly shorter, synthesis of vinyl epoxide **3.15** was developed from 1-chloro-2-butanone **3.29**, which was derived from methyl propionylacetate **3.27** according to a literature procedure.<sup>69</sup> Accordingly, **3.27** was chlorinated with sulfuryl chloride in  $\text{CH}_2\text{Cl}_2$  to give the mono-chlorinated product **3.28** (Scheme 3.7). Treatment of this material with 5 molar equiv. of 50% sulphuric acid under reflux accomplished cleavage of the methyl ester and concomitant decarboxylation of the resultant  $\beta$ -keto acid to give 1-chloro-2-butanone **3.29** as a colourless liquid in 72% yield after distillation. Addition of vinylmagnesium bromide to this compound formed chlorohydrin **3.30**. This compound proved to be somewhat unstable, decomposing if left at room temperature. However, if **3.30** was taken on crude and rapidly treated with ground KOH in  $\text{Et}_2\text{O}$ , vinyl epoxide **3.15** could be formed in 32% yield for the 2 steps. Although this route is not as robust as that starting from 1,2-butanediol, with the key cyclization proceeding in variable yield, it did allow production of over 10 g of **3.15** in 23% yield for the 4 steps.

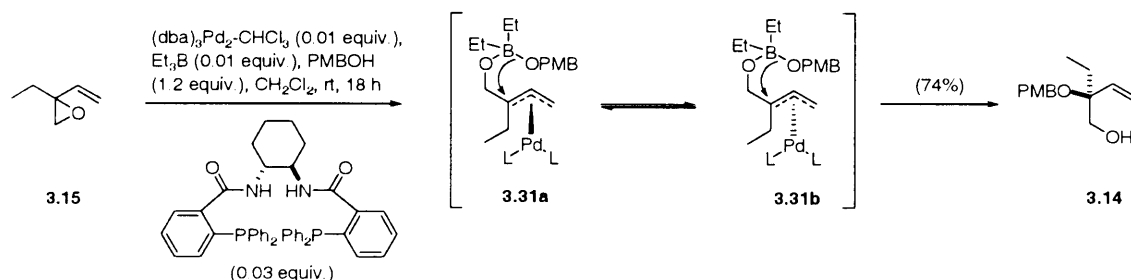


**Scheme 3.7** Synthesis of epoxide **3.15** from methyl propionylacetate **3.27**

With convenient large-scale routes to epoxide **3.15** established, the key step in our synthesis of aldehyde **3.5** could be attempted, namely a Trost asymmetric allylic alkylation (AAA) reaction.<sup>65</sup> This diverse class of asymmetric synthetic methodology has been developed by the Trost group over the past ten years, and encompasses a wide range of enantioselective transformations.<sup>66</sup> The AAA reaction has numerous mechanisms for enantiodiscrimination, and allows formation of C-H, C-N, C-O, C-S and C-C bonds.<sup>70</sup> The starting material can be achiral, prochiral or chiral racemic material, as in the case of epoxide **3.15**. The AAA reactions are generally catalysed by a chiral Pd(0) complex which promotes ionization of the starting material, an event that is followed by addition of the nucleophilic reacting partner.

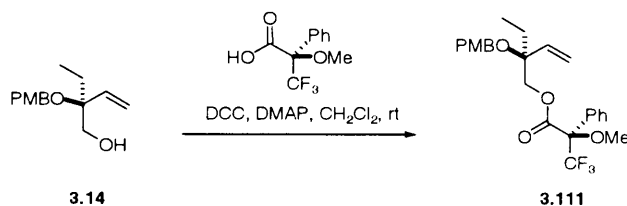
The AAA conversion of epoxide **3.15** to enantiopure alcohol **3.14** is co-catalysed by Et<sub>3</sub>B and a chiral palladium (0) complex formed between (dba)<sub>3</sub>Pd<sub>2</sub>-CHCl<sub>3</sub> and a chiral amide ligand derived from (*R,R*)-1,2-diaminocyclohexane and 2-diphenylphosphinobenzoic acid (Scheme 3.8). The chiral racemic epoxide forms a complex with the chiral Pd-catalyst, and is ionized and ring-opened to give the diastereomeric  $\pi$ -allylpalladium intermediates **3.31a** and **3.31b**. These intermediates can equilibrate via a  $\pi$ - $\sigma$ - $\pi$  equilibration mechanism, which is fast relative to the addition of the PMB-OH nucleophile. Either the most reactive or the most abundant of these intermediates leads to the enantiopure product **3.14**.





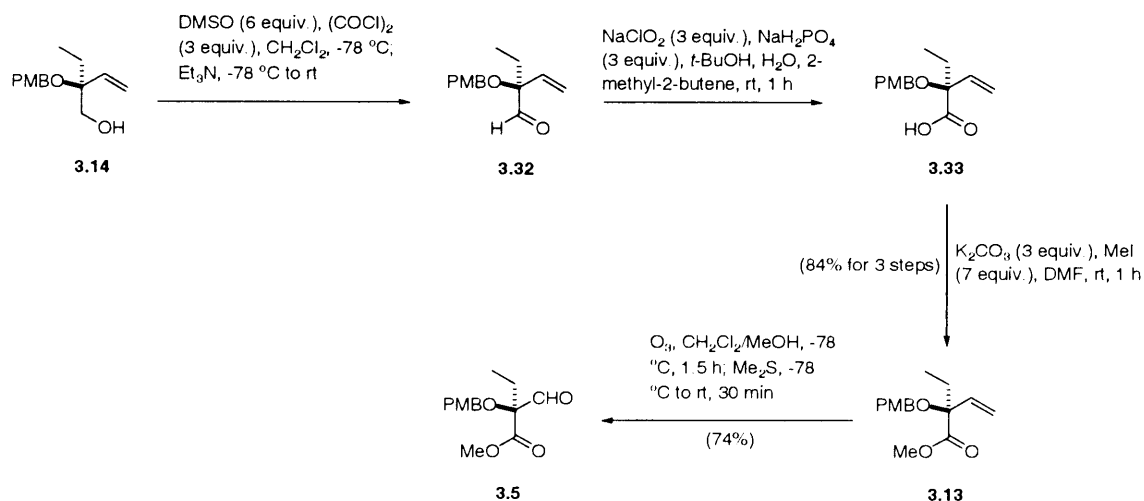
**Scheme 3.8** Trost asymmetric allylic alkylation of epoxide **3.15**

This type of selection, where the starting material is racemic, thus constitutes a dynamic kinetic asymmetric transformation, i.e. the maximum theoretical yield for the process is 100%, not 50% (as would be the case for a kinetic resolution). The borane co-catalyst serves to activate the primary alcohol (PMB-OH) nucleophile, and it also directs the addition to give the 1,2-hydroxy ether product, as opposed to the 1,4-addition product that might otherwise be favoured. Thus, this two-component catalytic system has the palladium activating the electrophile and boron, the nucleophile. The reaction is highly enantioselective, regioselective, and is also subtly chemoselective as the product alcohol **3.14** does not compete with the reactant PMB alcohol. On a practical level, the process is very easy to perform on a large scale. The chiral amide ligand,  $(dba)_3Pd_2-CHCl_3$  and PMB-OH were stirred together in anhydrous  $CH_2Cl_2$  for 5 minutes, with the formation of a dark red-orange solution indicating the creation of the active chiral Pd catalyst. The  $Et_3B$  co-catalyst was then added dropwise as a solution in THF, followed by the epoxide substrate **3.15**. This final addition was accompanied by a change in colour of the solution from dark red to an olive-yellow colour. The reaction mixture was then stirred at room temperature for 18 h, concentrated in vacuo and purified by flash chromatography on silica gel to give **3.14** in 74% yield. The ee was established as greater than 95% by formation of the Mosher ester by reaction of **3.14** with (*R*)-(+)- $\alpha$ -methoxy- $\alpha$ -(trifluoromethyl)phenylacetic acid ((+)-Mosher's acid) and DCC/DMAP in  $CH_2Cl_2$  (Scheme 3.9). Analysis of the  $^1H$  and  $^{19}F$  NMR spectra for the ester product **3.111** then determined the ee of the AAA reaction.



**Scheme 3.9** Mosher ester analysis of alcohol **3.14**

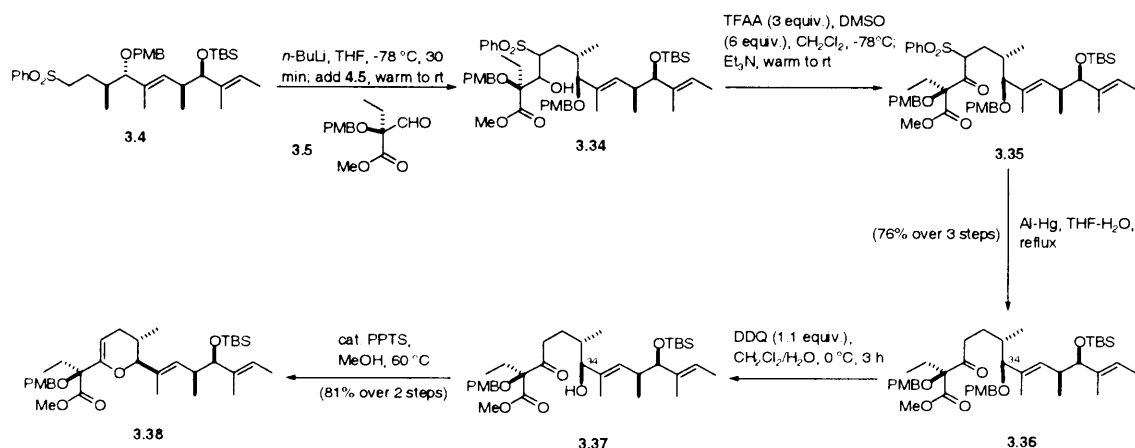
The derived alcohol **3.14** was then oxidized to carboxylic acid **3.33** by a two step procedure (Scheme 3.10). Firstly, a Swern oxidation gave aldehyde **3.32**, as confirmed by a singlet at 9.52 ppm in the 500 MHz  $^1\text{H}$  NMR spectrum in  $\text{CDCl}_3$ . This compound was then taken on crude and subjected to a Pinnick oxidation<sup>71</sup> with  $\text{NaClO}_2$  to give acid **3.33**, which appeared as a characteristic pink-purple streak on the reaction TLC plate. Alternatively, **3.14** could be oxidized directly to **3.33** by PDC in wet DMF, but this reaction was very slow and low yielding (~50%). Crude **3.33** was then methylated with  $\text{K}_2\text{CO}_3$  in DMF to furnish methyl ester **3.13** in a very healthy yield of 84% for the 3 steps. The material was generally stored at this point until aldehyde **3.5** was required for immediate use, it being formed by simple ozonolytic cleavage of the terminal carbon-carbon double bond of **3.13**. This step was carried out by bubbling ozone through a solution of **3.13** in  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  at  $-78^\circ\text{C}$ , with the solution turning light blue when the reaction was complete. After reductive cleavage of the intermediate ozonide with dimethyl sulfide, the highly functionalized aldehyde **3.5** was isolated in 74% after a rapid  $\text{SiO}_2$  chromatographic purification step. The 500 MHz  $^1\text{H}$  NMR spectrum of the product in  $\text{CDCl}_3$  showed a distinctive aldehydic proton resonance at 9.72 ppm. This route to aldehyde **3.5** was highly efficient, proceeding in 46% yield for the 5 steps from the bulk quantities of the readily available epoxide **3.15**.



**Scheme 3.10** Synthesis of aldehyde **3.5**

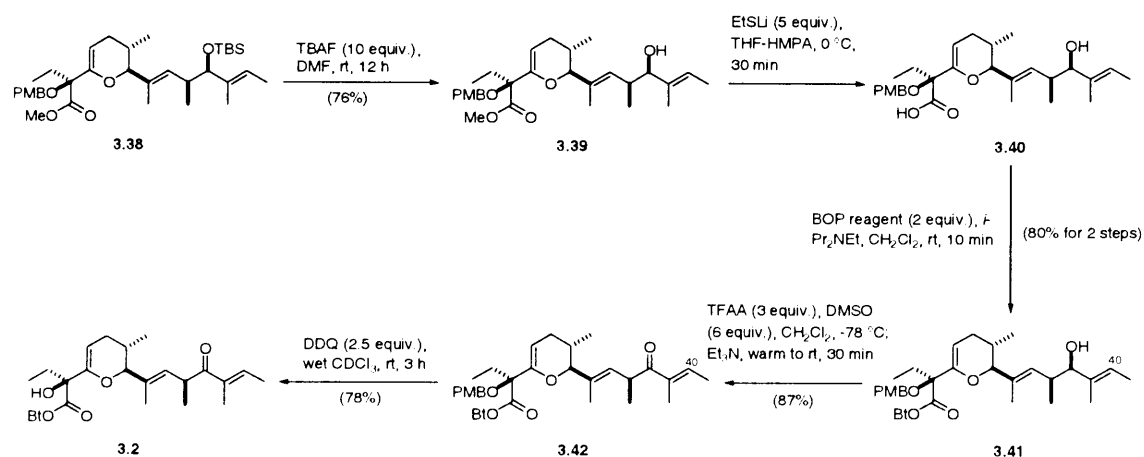
Aldehyde **3.5** was then condensed with the  $\alpha$ -phenylsulfonyl anion derived from sulfone **3.4** to give a mixture of  $\beta$ -hydroxysulfones **3.34** that underwent a Swern oxidation to afford the  $\beta$ -ketosulfones **3.34** (Scheme 3.11). Desulfonation of **3.35** proceeded efficiently with aluminium amalgam in aqueous THF to produce ketone **3.36** in 76% yield over the three steps. A resonance at 208.2 ppm in the 125 MHz  $^{13}\text{C}$  NMR spectrum in  $\text{CDCl}_3$  and a strong carbonyl absorption at  $1720\text{ cm}^{-1}$  in the IR spectrum indicated the presence of a ketone group within **3.36**.

Treatment of **3.36** with 1.2 equivalents of DDQ in aqueous  $\text{CH}_2\text{Cl}_2$  at  $0\text{ }^\circ\text{C}$  for 3 h accomplished a highly regioselective *O*-debenzylation at C(34) to furnish an  $\alpha/\beta$  mixture of ring-closed hemiketals in addition to linear hydroxyketone **3.37**. Exposure of this mixture to catalytic PPTS in MeOH at  $60\text{ }^\circ\text{C}$  effected a dehydrative ring-closure to give glycal **3.38** in 81% yield over two steps.<sup>34</sup>



**Scheme 3.11** Synthesis of glycal **3.38**

The next step was *O*-desilylation of **3.38** with excess TBAF in DMF at room temperature, which gave **3.39** in 76% yield (Scheme 3.12). The methyl ester was then detached from **3.39** with lithium ethanethiolate in THF/HMPA, and the crude acid **3.40** was converted into its hydroxybenzotriazole ester **3.41** with Hunig's base and the BOP reagent in  $\text{CH}_2\text{Cl}_2$  at room temperature in 80% yield for the two steps. After Swern oxidation with trifluoroacetic anhydride and DMSO, ketone **3.42** was isolated in 87% yield. This  $\alpha,\beta$ -unsaturated ketone appeared as a highly UV active spot on TLC, and gave a characteristic 500 MHz  $^1\text{H}$  NMR spectrum in  $\text{CDCl}_3$  with the chemical shift of the olefinic proton attached to C(40) appearing at 6.83 ppm, compared to a value of 5.43 ppm for the corresponding H atom of **3.41** in the same solvent. The PMB group was then excised from O(29) by exposure of **3.42** to 2.5 equivalents of DDQ in deuterated chloroform at room temperature for 3 h. Before the deprotected activated ester **3.2** could be used in any coupling reactions, it was essential to remove all traces of DDQ residues. This was accomplished by a rapid wash of the organic layer with aqueous  $\text{NaHCO}_3$  during the extraction, followed by a quick  $\text{SiO}_2$  flash chromatography purification step with 6:1 petrol/EtOAc as the eluent. This gave a 78% yield of **3.2**, which was used immediately as hydration of the glycal would occur upon exposure to moisture.



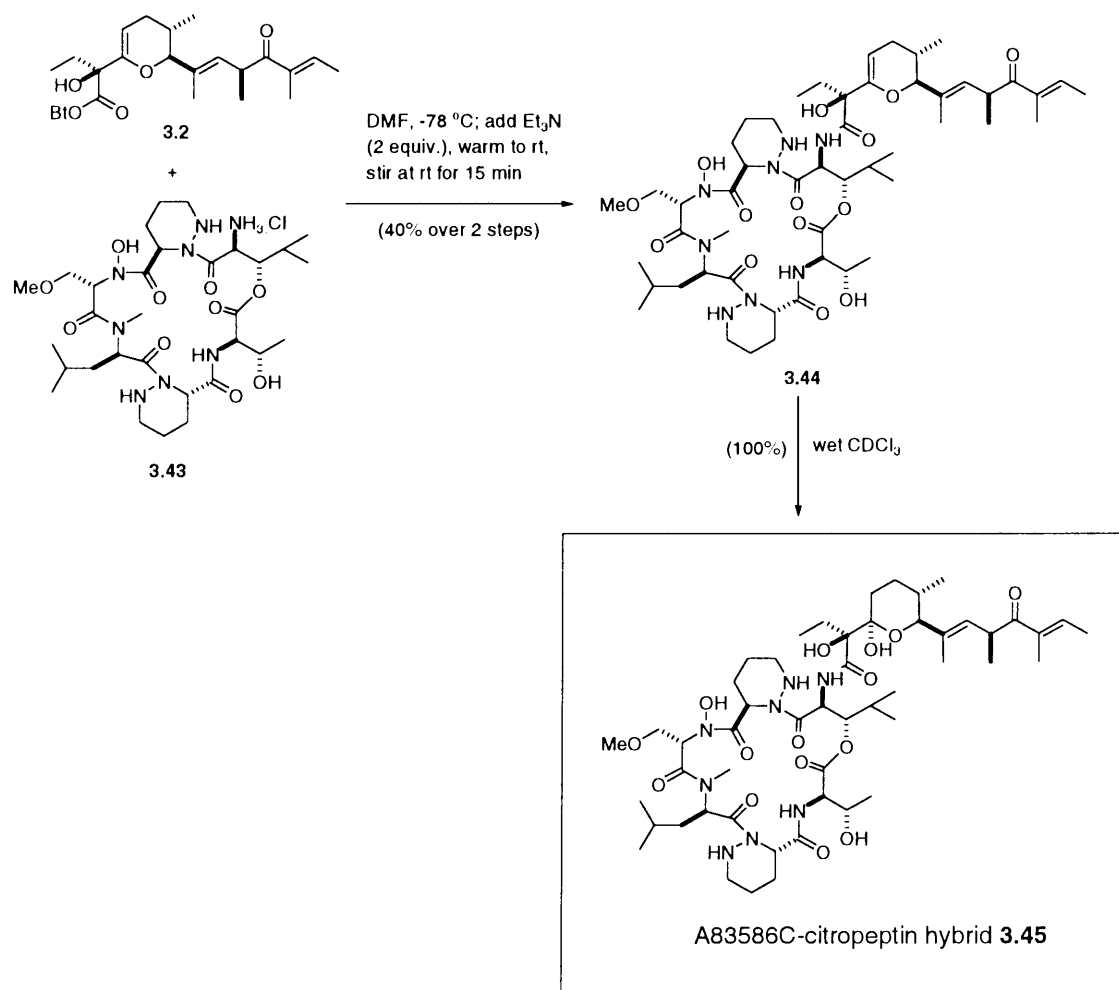
**Scheme 3.12** Synthesis of activated ester **3.2**

### 3.1.3 Synthesis of an A83586C-citropeptin hybrid molecule

With a good supply of the activated ester of the A83586C acyl side chain now available, the synthesis of the A83586C-citropeptin hybrid **3.45** was reinvestigated. This analogue has been shown to potently upregulate TCF4 expression and downregulate  $\beta$ -catenin at 10 nM concentration in metastatic Rama-37-OPN mammary epithelial cells, consequently causing a 77% reduction in osteopontin expression.

The key coupling reaction between the A83586C activated ester **3.2** and the citropeptin cyclodepsipeptide hydrochloride salt **3.43** (which has previously been synthesized by M. Walters in the Hale laboratory<sup>72</sup>) was carried out by mixing the two reactants in a flask, adding anhydrous DMF, cooling to -78 °C, and then adding 2 equiv. of Et<sub>3</sub>N (Scheme 3.13). The reaction mixture was stirred at -78 °C for 10 min, and then gradually warmed to room temperature over 30 min. After work up, the coupled product **3.44** was purified by preparative TLC and SiO<sub>2</sub> flash chromatography, and then dissolved in wet CDCl<sub>3</sub> to give the hydrated product **3.45** in 40% yield from the benzyl-protected precursor of salt **3.43**. This yield may appear modest, but it actually represents the combined yield for the final three steps of the synthesis (benzyl group deprotection, coupling, hydration). The average yield for these challenging final steps is therefore a healthy 74%. The <sup>1</sup>H and <sup>13</sup>C NMR spectra of **3.45** matched those previously obtained by M. Walters of this laboratory.<sup>72</sup> The yield of this

coupling represents a considerable improvement compared to the corresponding sequence in the A83586C synthesis, a fact that renders the hybrid **3.45** a possibly more attractive candidate for development as an anti-tumour agent than A83586C.

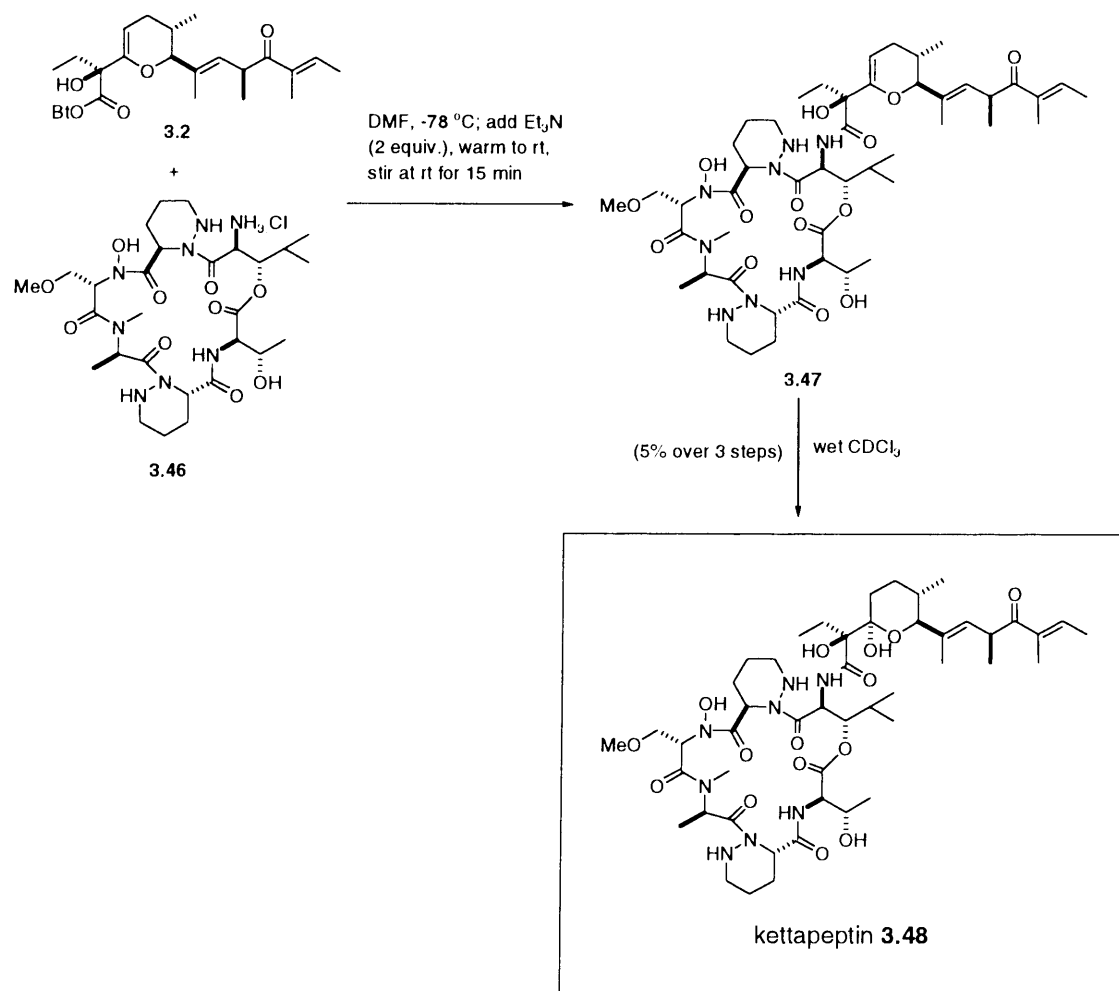


**Scheme 3.13** Synthesis of A83586C-citropeptin hybrid **3.45**

### 3.1.4 Total synthesis of kettapeptin

The A83586C activated ester **3.2** was reacted with the azinothricin cyclodepsipeptide hydrochloride salt **3.46**, which has recently been made by the Hale group<sup>72</sup> to generate an A83586C-azinothricin hybrid molecule. However, in this case the coupled product **3.48** was isolated in a highly disappointing yield of 5% with a number of chromatographic purification steps being necessary to obtain the pure product (Scheme 3.14). Analysis of the NMR and IR

data for **3.46** indicated that the problem here probably lay in the purity of this cyclodepsipeptide; the synthesis of this molecule needs to be reinvestigated.



**Scheme 3.14** Synthesis of kettapeptin **3.48**

The initial aim of this experiment was to synthesize an A83586C-azinothricin hybrid molecule. However, in 2006 this molecule was isolated from *Streptomyces* GW99/1572 by Laatsch and co-workers, and was named kettapeptin. The structure of kettapeptin was rigorously determined by NMR studies and crystal structure analysis. Our work thus represents the first total synthesis of this novel natural product. The <sup>1</sup>H and <sup>13</sup>C NMR data we obtained from our synthetic kettapeptin showed an excellent correlation with the Laatsch group data (see Table 3.1). The distinctive <sup>13</sup>C signal for C(30) at 99.6 ppm was observed, indicating that complete

hydration of the glycal motif had been achieved. HRMS showed the presence of an  $[M+Na]^+$  ion at  $m/e$  1029.5484 which confirmed the empirical formula  $C_{48}H_{76}N_8O_{15}$ .

C No.	Natural kettapeptin	Synthetic kettapeptin	C No.	Natural kettapeptin	Synthetic kettapeptin
1	170.2	170.3	25	19.3	19.4
2	56.2	56.2	26	14.6	14.7
3	169.5	169.6	27	29.4	29.5
4	52.4	52.5	28	175.3	175.3
5	24.4	24.4	29	80.1	80.1
6	21.3	21.3	30	99.6	99.6
7	48.0	48.0	31	28.3	28.3
8	173.1	173.1	32	27.2	27.3
9	47.7	47.7	33	32.5	32.6
10	171.0	171.1	34	82.2	82.2
11	53.8	53.9	35	132.8	132.8
12	172.8	172.8	36	129.3	129.4
13	51.3	51.3	37	38.2	38.2
14	24.0	24.0	38	203.0	202.9
15	21.1	21.1	39	137.5	137.5
16	45.6	45.7	40	136.8	136.7
17	170.8	170.9	41	14.9	14.8
18	54.6	54.7	42	25.9	25.9
19	78.6	78.7	43	8.4	8.3
20	64.7	64.8	44	17.6	17.6
21	18.9	18.9	45	12.0	12.1
22	13.1	13.2	46	19.5	19.5
23	68.5	68.5	47	11.4	11.4
24	29.2	29.3	48	59.2	59.2

**Table 3.1** Comparison of the  $^{13}\text{C}$  (150 MHz) NMR data in  $\text{CDCl}_3$  for natural kettapeptin<sup>8</sup> with the  $^{13}\text{C}$  (125 MHz) NMR data in  $\text{CDCl}_3$  obtained for **3.48**

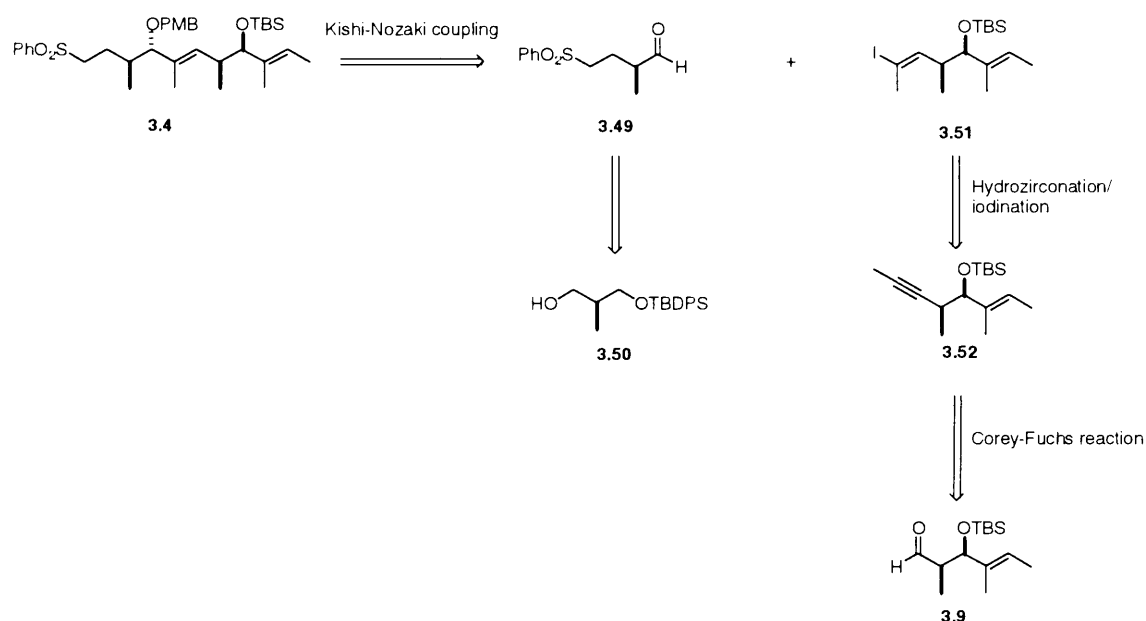
## 3.2 Alternative synthetic approaches to the acyl side chain of A83586C

### 3.2.1 Synthetic strategy based on a Kishi-Nozaki coupling as the key step

During our synthetic studies towards the acyl side chain of A83586C we investigated a number of alternative routes to the key sulfone **3.4**. The first of these involved a Kishi-Nozaki coupling<sup>73</sup> between vinyl iodide **3.51** and aldehyde **3.49** as the key step (Scheme 3.15). The

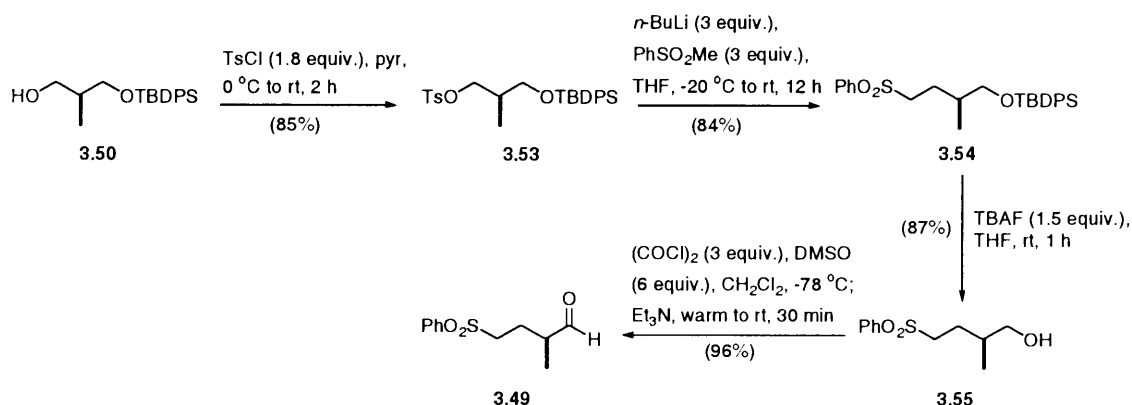


known aldehyde **3.49** could be accessed from alcohol **3.50**, a compound derived from commercially available (*R*)-methyl 3-hydroxy-2-methylpropionate (Roche's ester). It was envisaged that the vinyl iodide coupling partner could be obtained from terminal alkyne **3.52** via a hydrozirconation-iodination procedure.<sup>74</sup> The methyl acetylene **3.52** could be formed from aldehyde **3.9** by a Corey-Fuchs reaction.<sup>75</sup> Aldehyde **3.9** was obviously available via the asymmetric aldol reaction route previously described.



**Scheme 3.15** Retrosynthetic analysis of sulfone **3.4** based on a Kishi-Nozaki coupling as the key step

Synthesis of aldehyde **3.49** followed the method published by Mulzer in 2000.<sup>76</sup> The route commenced with tosylation of alcohol **3.50** with tosyl chloride in pyridine (Scheme 3.16). The resultant tosylate **3.53** was then alkylated with methyl phenyl sulfone anion to furnish sulfone **3.54** in 84% yield. Removal of the TBDPS protecting group with TBAF in THF unveiled the primary alcohol functionality of **3.55**, which was oxidized to aldehyde **3.49** by a Swern reaction with oxalyl chloride and DMSO in CH<sub>2</sub>Cl<sub>2</sub>.

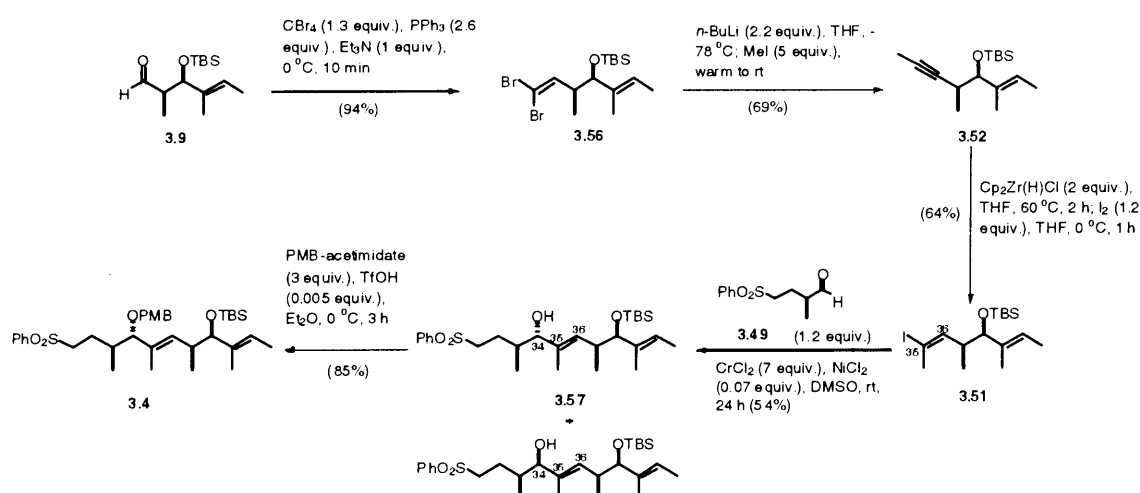


**Scheme 3.16** Synthesis of aldehyde **3.49**

Aldehyde **3.9** was transformed into the highly non-polar dibromide **3.56** following the Corey-Fuchs protocol<sup>75</sup> (Scheme 3.17). The reaction of this dibromide with two equivalents of *n*-BuLi in THF at -78 °C resulted in the rapid formation of the corresponding acetylide anion, which was subsequently quenched with methyl iodide to generate the methyl acetylene derivative **3.52** in 69% yield. In the next step compound **3.52** was treated with commercially available bis(cyclopentadienyl)zirconium chloride hydride (the Schwartz reagent<sup>77</sup>) in THF heated at reflux for 2 h to generate an organozirconium intermediate by a hydrozirconation reaction. This intermediate was quenched with I<sub>2</sub> at 0 °C to furnish the vinyl iodide **3.51** in 64% yield. The organozirconium species is formed with high (*E*)-selectivity and regioselectivity (with the bulky zirconocene moiety adding to the least hindered position of the carbon-carbon triple bond), and this stereoselectivity is retained in the vinyl iodide product. The choice of solvent for the hydrozirconation step was found to be crucial, with the use of CH<sub>2</sub>Cl<sub>2</sub> or benzene giving far lower stereoselectivity than THF. An attempt to directly couple the organozirconium intermediate with the aldehyde **3.49** via a Zr to Zn transmetalation protocol developed by Wipf<sup>78</sup> was unsuccessful. This is perhaps unsurprising, as to date, this type of chemistry has only been applied to terminal alkynes for the formation of disubstituted alkenes, such as in Wipf's synthesis of Curacin A.<sup>79</sup>

With vinyl iodide **3.51** and aldehyde **3.49** now in hand, the stage was set for their unification by a Kishi-Nozaki coupling.<sup>73</sup> This reaction is mediated by stoichiometric Cr(II) and catalytic Ni(II), which combine in a catalytic cycle to transform the vinyl iodide into a nucleophilic Cr(III)

species. This reactive intermediate is highly chemoselective, combining only with an aldehyde as the electrophilic reaction partner. In the case of this synthesis, iodide **3.51** and aldehyde **3.49** were stirred together with 7 equivalents of Cr(II)Cl<sub>2</sub> contaminated with 0.1% Ni(II)Cl<sub>2</sub> in DMSO for 24 h at room temperature. This gave the coupled product **3.57** as the major component of a 1.5:1 mixture of C(34) epimers in combined yield of 54%. Importantly, the (*E*)-stereochemistry of the C(35)-C(36) double bond was maintained in the coupled product. The desired stereoisomer **3.57** could be separated from the undesired by a careful flash chromatography step. The stereochemistry of **3.57** was confirmed by protection of the free hydroxyl as a PMB group to form **3.4**, which allowed correlation with the previous synthetic work.

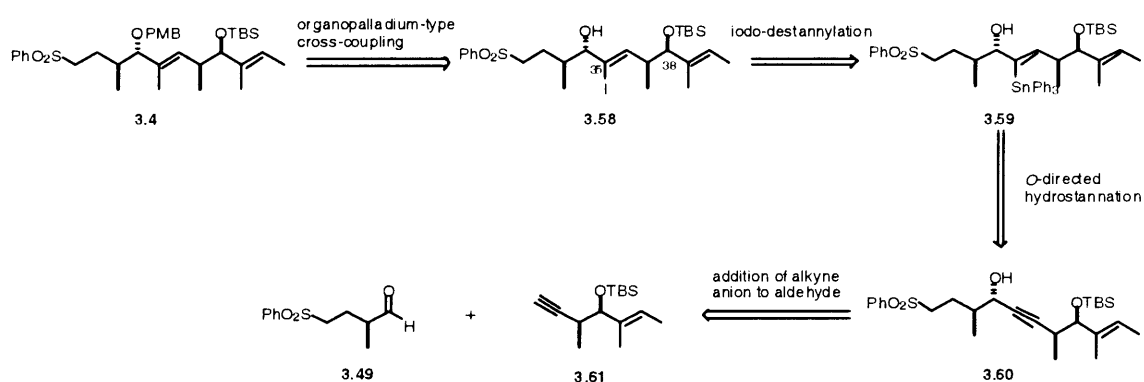


**Scheme 3.18** Synthesis of sulfone **3.4** by a Kishi-Nozaki reaction

The low and poor stereoselectivity of the key Kishi-Nozaki coupling dictated that this route was not an ideal method for synthesis of sulfone **3.4** on a large scale. Furthermore, both the hydrozirconation and Kishi-Nozaki steps proceeded in variable yields when conducted on a large scale; in this context, they are not robust processes. Indeed, most applications of the Kishi-Nozaki protocol in total synthesis<sup>80</sup> are delicate late-stage operations that often proceed in relatively low yield. The expense of the Schwartz reagent and Cr(II)Cl<sub>2</sub> was another negative factor, as both are required in stoichiometric quantities.

### 3.2.2 Synthetic strategy based on an *O*-directed hydrostannation reaction as the key step in assembly of the C(35)-C(36) trisubstituted olefin

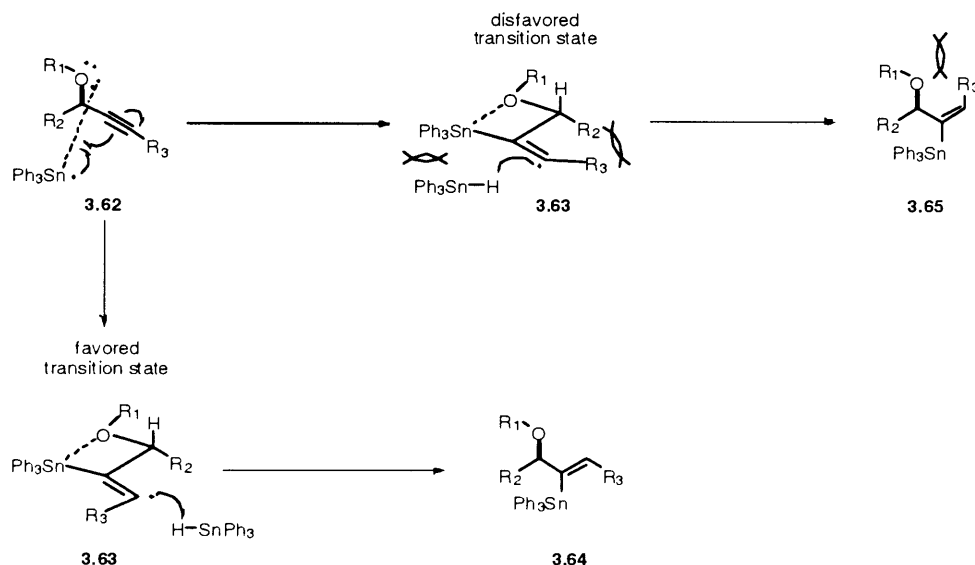
A second alternative retrosynthetic analysis of sulfone **3.4** was conceived where an *O*-directed hydrostannation reaction featured as the key step (Scheme 3.18). In this strategy, it was envisaged that sulfone **3.4** would be formed from vinyl iodide **3.58** by a Stille<sup>81</sup> or Negishi-type<sup>82</sup> Pd-catalysed cross-coupling reaction. Iodide **3.58** would be derived from iodo-destannylation of vinylstannane **3.59**, which could in turn be formed by a stereo- and regioselective *O*-directed free radical hydrostannation of alkynol **3.60** with  $\text{Ph}_3\text{SnH}$  and catalytic  $\text{Et}_3\text{B}$ .<sup>83</sup> Addition of the acetylide anion of **3.61** to the known aldehyde **3.49** would allow convenient access to alkynol **3.60**. A possible advantage of this synthetic strategy would be the potential for diversification at C(35), with use of different halide cross-coupling partners yielding alternative analogue structures. However, a possible stumbling block was the fact that the vinyl iodide motif **3.58** is quite hindered, and an earlier attempt at elaborating a similar enol triflate had failed. However, in the present instance, an OTBS rather than an OTBDPS would be present at C(38), which might expedite oxidative addition.



**Scheme 3.18** Retrosynthetic analysis of sulfone **3.4** based on an *O*-directed hydrostannation as the key step

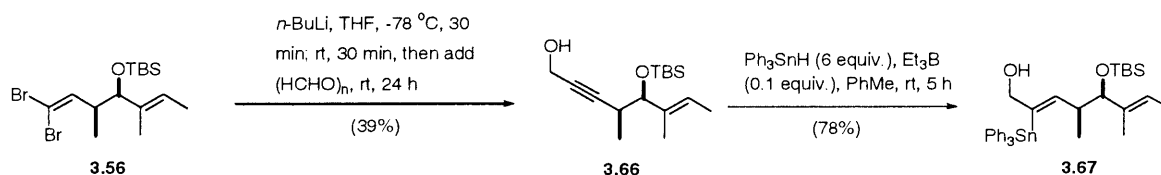
The *O*-directed free radical hydrostannation of disubstituted acetylenes with  $\text{Ph}_3\text{SnH}$  and catalytic  $\text{Et}_3\text{B}$  in PhMe at room temperature is a novel reaction system that has recently been developed by the Hale group.<sup>83,84,85</sup> The reaction is highly regio- and stereoselective, and

represents a considerable improvement over existing thermally mediated *O*-directed hydrostannation methodologies involving Bu<sub>3</sub>SnH and AIBN, which require more vigorous conditions and are of limited practical use. During the design of the new reaction system, it was anticipated that the enhanced Lewis acidity of Ph<sub>3</sub>SnH compared to Bu<sub>3</sub>SnH would allow the former to coordinate to the *O*-atom of propargylically oxygenated alkyl acetylenes far more effectively than the latter. It was also expected that *O*-coordinated Ph<sub>3</sub>SnH would more readily undergo H-atom abstraction than uncoordinated Ph<sub>3</sub>SnH, and that *O*-coordinated triphenylstannyl radicals would have a longer lifetime in solution compared with their uncoordinated counterparts. It was reasoned that the regioselectivity of the addition of the tin unit to the  $\alpha$ -acetylenic carbon atom of **3.62** would be improved by the creation of this longer-lived *O*-coordinated tin radical (Scheme 3.19). It was further postulated that if Ph<sub>3</sub>SnH was employed for hydrostannation (as opposed to Bu<sub>3</sub>SnH), greatly magnified steric effects would operate in the vinyl radical H-atom abstraction step, owing to the bent nature of alkylvinyl radicals **3.63** and the probability that such radicals would abstract hydrogen from the stannane via a transition state that would minimize steric repulsions between the bulky Ph<sub>3</sub>Sn group of **3.63** and the incoming stannane, while simultaneously avoiding A<sup>1,3</sup> strain (Scheme 3.19). The result of these factors should be that the transition state leading to **3.64** is considerably more favoured with Ph<sub>3</sub>SnH than the corresponding one with Bu<sub>3</sub>SnH. Thus, use of Ph<sub>3</sub>SnH would lead to greater regioselectivity ( $\alpha$ - addition) and stereoselectivity (to give the (*Z*)-alkenyl product).



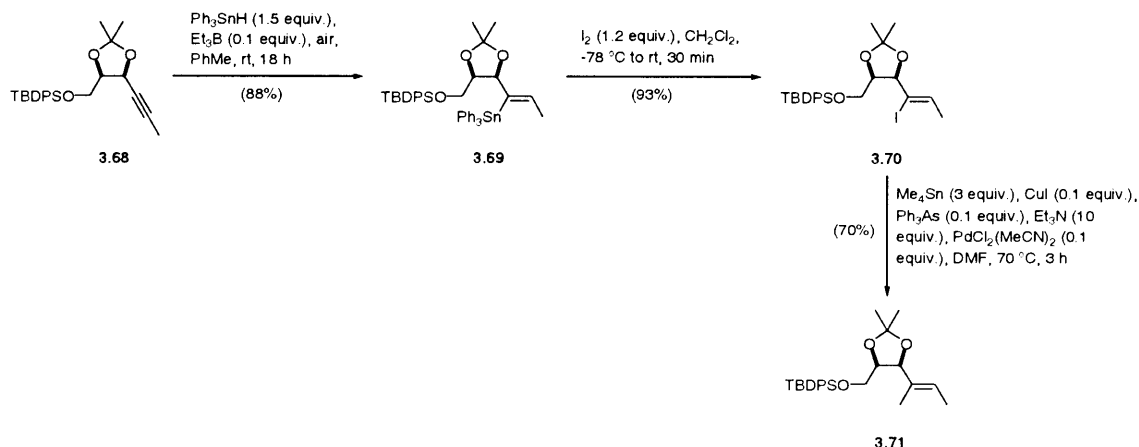
**Scheme 3.19** Transition states for *O*-directed hydrostannation of disubstituted alkynes

The Hale hydrostannation reaction conditions have indeed been used to prepare a wide range of vinylstannanes in high yield and with excellent regio- and stereoselectivity.<sup>83</sup> A model reaction relevant to the studies towards the A83586C side chain was conducted, as shown in Scheme 3.20, in which alkynol **3.66** (obtained from dibromide **3.56**) was observed to undergo selective hydrostannation to give **3.67**.<sup>85</sup> In this case, a high concentration of triphenyltin radicals (6 equivalents of  $\text{Ph}_3\text{SnH}$ , 0.1 M in PhMe) is necessary to ensure selective addition to the  $\alpha$ -acetylenic carbon of **3.66**. At lower concentrations, reversible  $\beta$ -addition occurs, which in this substrate forms a vinyl radical that is primed to undergo a 5-*exo-trig* cyclization.



**Scheme 3.20** Model hydrostannation of alkynol **3.66**

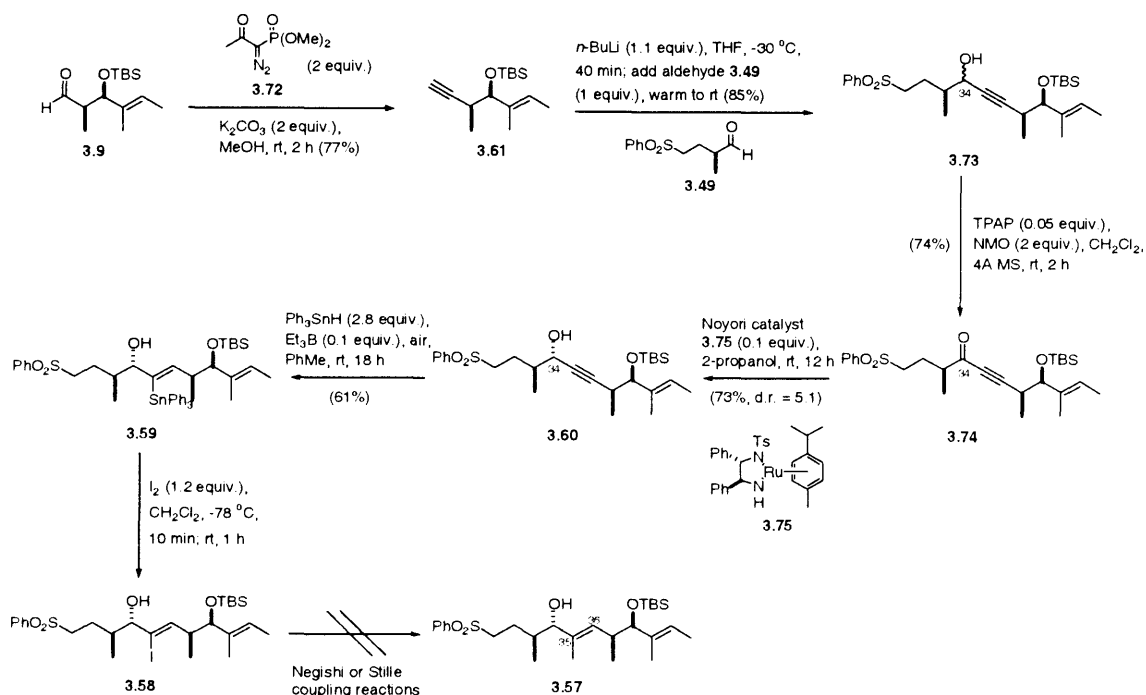
In order for the *O*-directed hydrostannation to be synthetically useful, it was necessary to demonstrate that the trisubstituted vinyltriphenylstannane products could be stereospecifically converted into stereodefined trisubstituted alkenes via an iododestannylation reaction.



**Scheme 3.21**  $\text{sp}^3/\text{sp}^2$ -Stille coupling of vinyl iodide **3.70** to give trisubstituted alkene **3.71**

As shown in Scheme 3.21, stannane **3.69** was formed from methyl acetylene **3.68** by a regio- and stereoselective hydrostannation, and this compound underwent tin-iodine exchange with  $\text{I}_2$  in  $\text{CH}_2\text{Cl}_2$  at  $-78^\circ\text{C}$  with complete retention of configuration to give vinyl iodide **3.70**. This compound participated in a  $\text{Pd}(0)$ -mediated  $\text{sp}^3/\text{sp}^2$ -Stille cross coupling with  $\text{Me}_4\text{Sn}$  in the presence of copper(I) iodide and triphenylarsine in DMF at  $100^\circ\text{C}$  to give trisubstituted alkene **3.71**.<sup>84</sup>

With the synthetic usefulness of the *O*-directed hydrostannation established, an attempt was made to apply the reaction to the construction of the C(35)-C(36) (*E*)-double bond of sulfone **3.4** (Scheme 3.22). The first step of this route was conversion of aldehyde **3.9** into terminal alkyne **3.61** using the Ohira reagent<sup>86</sup> **3.72** according to the conditions of Bestmann<sup>87</sup>. This reaction proceeded in 77% yield to give the product alkyne as a runny liquid after chromatographic purification. Alkyne **3.61** was then lithiated with *n*-BuLi in THF at  $-30^\circ\text{C}$  to give the corresponding acetylide anion, addition of which to the known aldehyde **3.49** furnished alkynol **3.73** in 85% yield.



**Scheme 3.22** Attempted synthesis of **3.57** by application of *O*-directed hydrostannation

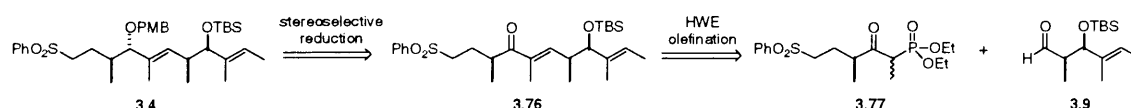
Despite the  $\alpha$ -stereocentre of aldehyde **3.49**, the addition proceeded without any stereochemical bias, and **3.73** was formed as a 1:1 inseparable mixture of C(34) epimers, appearing as one spot on TLC. This mixture was oxidized to a single compound, alkynyl ketone **3.74**, with catalytic TPAP<sup>88</sup> and stoichiometric NMO in  $\text{CH}_2\text{Cl}_2$  at room temperature. Formation of the desired C(34) stereochemistry was then investigated by application of Noyori's asymmetric transfer hydrogenation,<sup>89</sup> a reaction that has found several recent applications in total synthesis.<sup>90</sup> Accordingly, alkynyl ketone **3.74** was treated with 0.1 equiv. of the (*S,S*)-Noyori catalyst **3.75**<sup>91</sup> in propan-2-ol to give propargylic alcohol **3.60** as the major product in a d.r. of 5:1. This material was then subjected to the key *O*-directed hydrostannation with 2.8 equiv. of  $\text{Ph}_3\text{SnH}$ , 0.1 equiv. of triethylborane in PhMe at a concentration of 0.2 M with respect to **3.60**. This gave vinylstannane **3.59** in 66% yield after  $\text{SiO}_2$  flash chromatographic purification, although some Sn impurities were still present at this stage. Iodo-destannylation of **3.59** was accomplished with  $\text{I}_2$  in  $\text{CH}_2\text{Cl}_2$  at  $-78^\circ\text{C}$  to give vinyl iodide **3.58** in 64% yield as a single stereoisomer. However, at this point we met with disappointment, as elaboration of the vinyl iodide into trisubstituted alkene **3.57** proved impossible by the Stille and Negishi-type Pd(0)-catalysed cross-couplings that we attempted.



Again, the vinyl iodide functional group must be too hindered to undergo the oxidative addition step of the catalytic cycle, and even use of the more reactive vinyltri-*n*-butylstannane failed to give any coupled product.

### 3.2.3 Synthetic strategy based on a Horner-Wadsworth-Emmons reaction as the key step

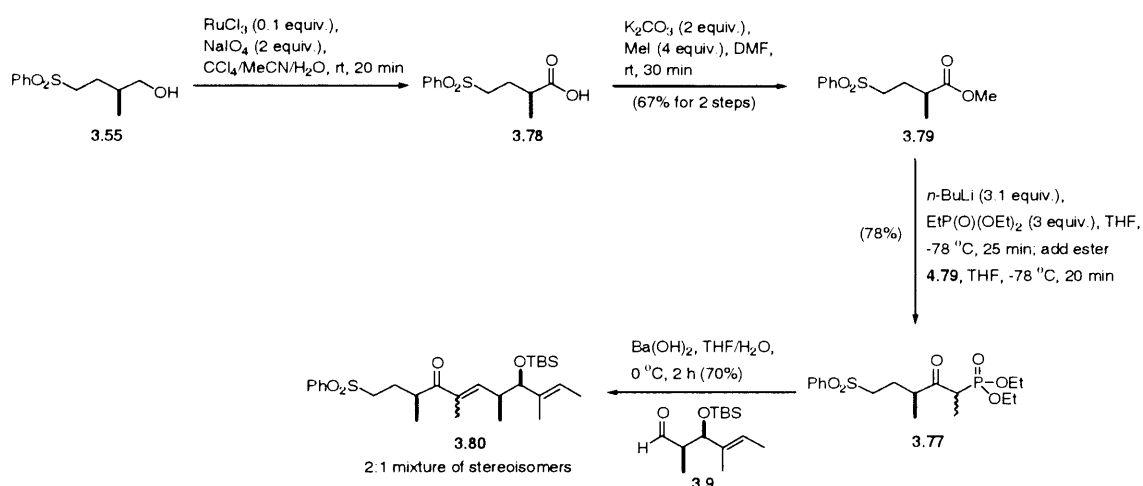
A third alternative strategy for the synthesis of the key sulfone **3.4** was designed with a key Horner-Wadsworth-Emmons reaction<sup>92</sup> planned between  $\beta$ -ketophosphonate **3.77** and aldehyde **3.9** to form the C(35)-C(36) carbon-carbon double bond (Scheme 3.23). Stereoselective reduction of  $\alpha,\beta$ -unsaturated ketone **3.76** and protection of the resultant hydroxyl would then give **3.4**. The Horner-Wadsworth-Emmons reaction, a versatile method for the formation of  $\alpha,\beta$ -unsaturated ketones, has seen extensive use in natural product synthesis,<sup>93</sup> and we expected it would work well in this situation.



**Scheme 3.23** Retrosynthetic analysis analysis of sulfone **4.4** based on a Horner-Wadsworth-Emmons olefination as the key step

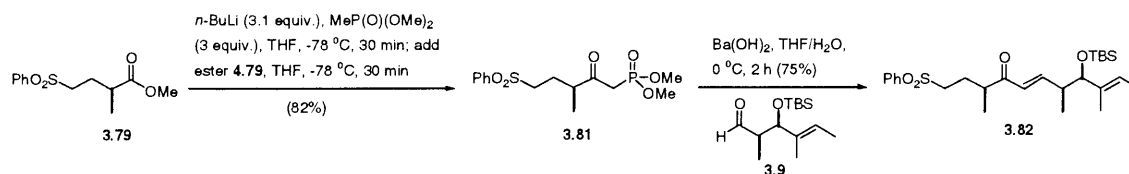
Alcohol **3.55** was oxidized with  $\text{RuCl}_3/\text{NaIO}_4$  to give carboxylic acid **3.78**, and esterification of this crude material with  $\text{K}_2\text{CO}_3/\text{MeI}$  in DMF at room temperature furnished **3.79** in a yield of 67% over the two steps (Scheme 3.24). Methyl ester **3.79** was treated with the lithium salt of diethyl ethylphosphonate to give  $\beta$ -ketophosphonate **3.77** as a 1:1 mixture of C(35) diastereomers. At this juncture, we attempted to engage **3.77** with aldehyde **3.9** in a Horner-Wadsworth-Emmons reaction. Initial efforts at performing this coupling by conventional methods (e.g.  $\text{NaH}$  or  $n\text{-BuLi}$  in THF) or by the milder Roush-Masamune protocol<sup>94</sup> ( $\text{LiCl}$ ,  $i\text{-PrNEt}_2$  or  $\text{Et}_3\text{N}$ , MeCN) gave unsatisfactory results, with either poor conversion or competing  $\beta$ -elimination in the aldehyde **3.9**. Application of Paterson's conditions<sup>95</sup> (0.8 equiv. of

Ba(OH)<sub>2</sub> in aqueous THF) accomplished smooth construction of the key C(35)-C(36) carbon-carbon double bond, although an inseparable 2:1 mixture of (*E*)- and (*Z*)-stereoisomers was formed. Unfortunately, the use of various different inorganic bases (e.g. LiOH), solvents and reaction temperatures failed to improve the selectivity of this process.



**Scheme 3.24** Synthesis of  $\alpha,\beta$ -unsaturated ketone **3.80** as a 2:1 mixture of stereoisomers

(*E*)/(*Z*)-selectivity in the formation of trisubstituted alkenes by Horner-Wadsworth-Emmons olefination is known to be a troublesome issue.<sup>96</sup> However, Ba(OH)<sub>2</sub>-mediated synthesis of the disubstituted  $\alpha,\beta$ -unsaturated ketone analogue **3.82** from  $\beta$ -ketophosphonate **3.81** and aldehyde **3.9** proceeded with complete (*E*)-selectivity and 75% yield (Scheme 3.25). This model study illustrated the unsuitability of the Horner-Wadsworth-Emmons based strategy for the synthesis of the A83586C side chain, due to unselective formation of the C(35)-C(36) trisubstituted carbon-carbon double bond.

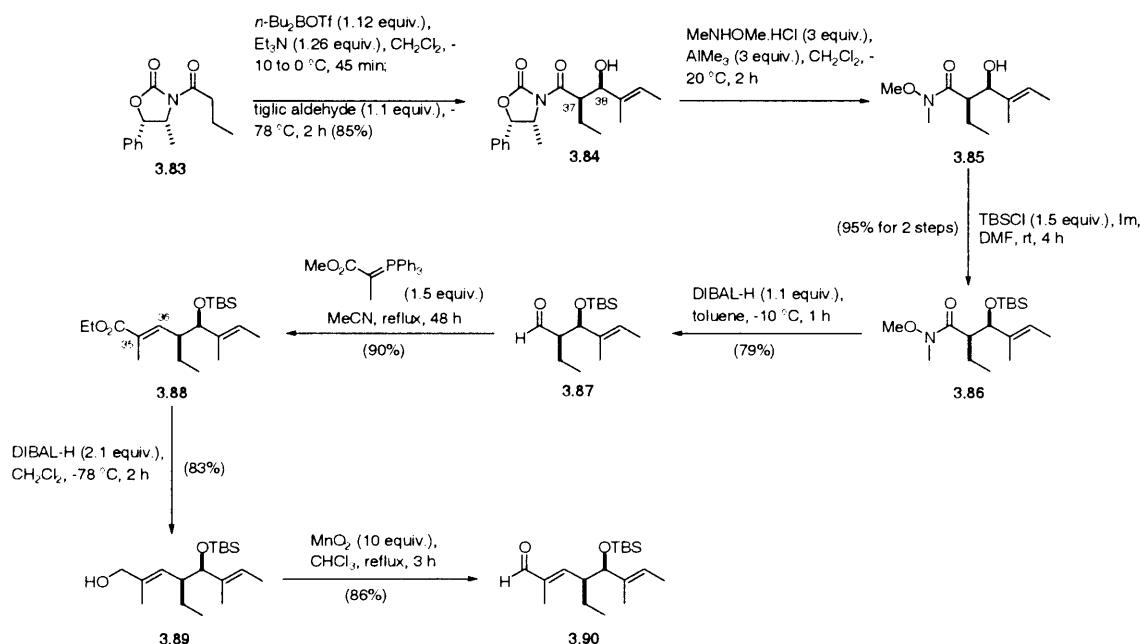


**Scheme 3.25** Synthesis of  $\alpha,\beta$ -unsaturated ketone **3.82**

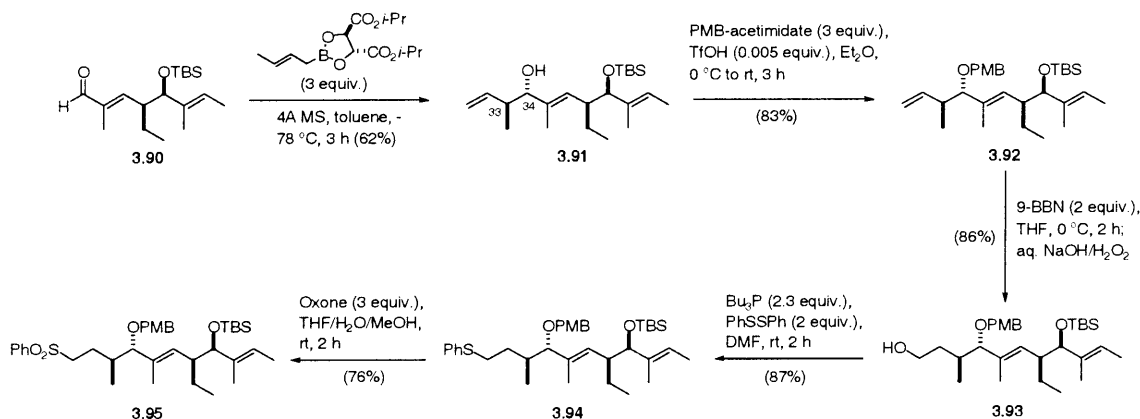
### 3.3 Total synthesis of azinothricin

With a scaleable, robust route to the A83586C acyl side chain established that was based on successive use of stereoselective aldol, Wittig and crotylation reactions to form sulfone **3.4** (Schemes 3.4 and 3.5) and an asymmetric allylic alkylation to form aldehyde **3.5** (Schemes 3.8 and 3.10), it was logical to apply this strategy to a synthesis of the azinothricin side chain, with the ultimate goal of the first total synthesis of azinothricin itself firmly in mind. This side chain differs from that of A83586C in the presence of an ethyl group at C(37) in place of a methyl group. The azinothricin side chain activated ester could then be used to synthesize some hybrid structures, as well as the azinothricin natural product itself.

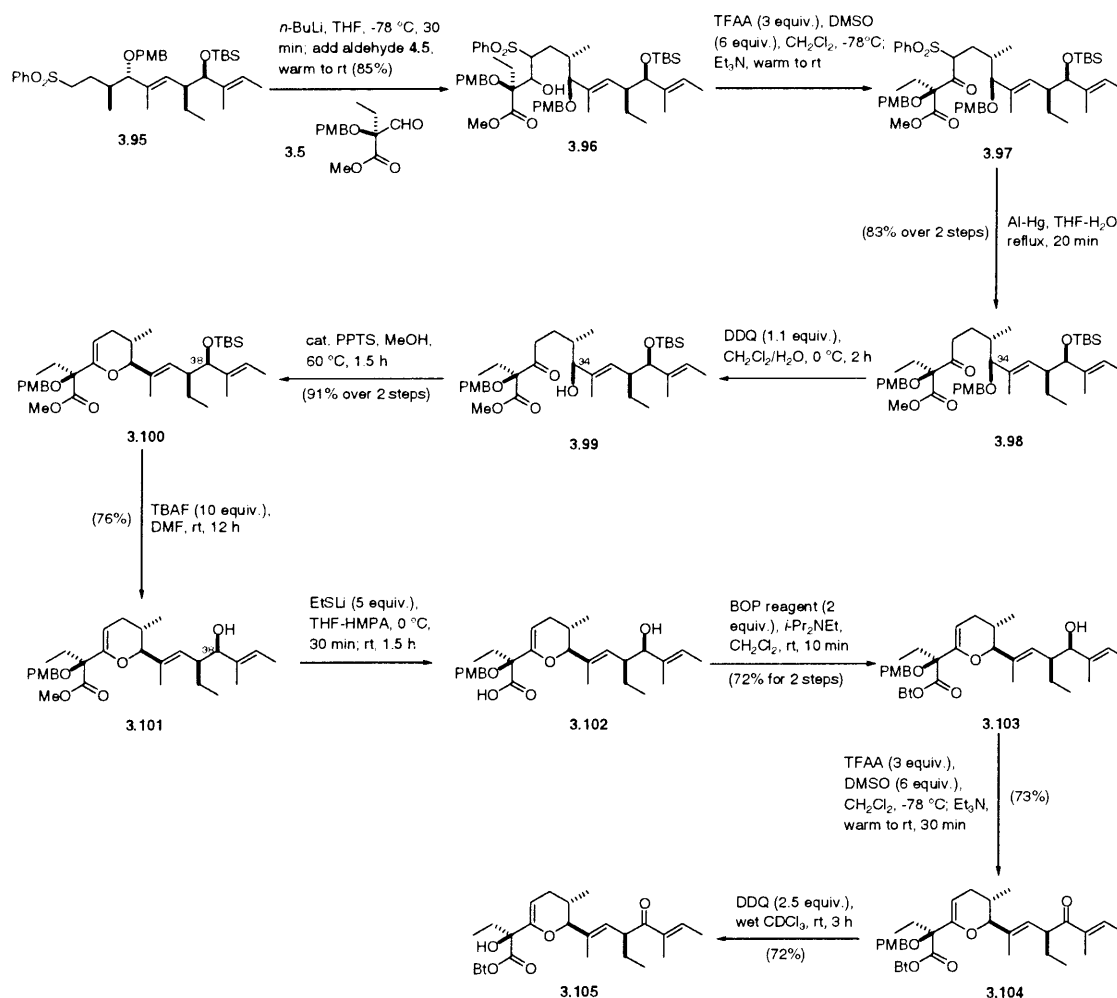
The chemistry involved in the route to the azinothricin acyl side chain was analogous to that of the A83586C synthesis described previously, so it will only be briefly discussed here. The first step was again an Evans' asymmetric aldol reaction, but in this case the (*Z*)-enolate derived from *N*-butyryl-2-oxazolidinone **3.83** was used in the addition to tiglic aldehyde (Scheme 3.26). This gave the aldol adduct **3.84** with selective formation of the C(37)-C(38) *syn*-stereochemistry. Transamination with *N,O*-dimethylhydroxylamine, TBS-protection and DIBAL-H reduction steps gave aldehyde **3.87** in 75% for the 3 steps. An (*E*)-selective Wittig reaction between this aldehyde and (carbethoxyethylidene)triphenylphosphorane successfully installed the C(35)-C(36) double bond to form  $\alpha,\beta$ -unsaturated ester **3.88** in 90% yield. Reduction of this compound to the allylic alcohol **3.89** with DIBAL-H (83%) was followed by MnO<sub>2</sub>-mediated oxidation to give the  $\alpha,\beta$ -unsaturated aldehyde **3.90** (86%).

Scheme 3.26 Synthesis of aldehyde **3.90**

The synthesis continued with aldehyde **3.90** participating in an asymmetric crotylboration with Roush's (*R,R*)-diisopropyl tartrate (*E*)-crotylboronate to set the C(33)-C(34) *anti*-stereochemistry and give allylic alcohol **3.91** as a 2.3:1 mixture of diastereomers (Scheme 3.26). Careful separation of these compounds by flash chromatography furnished pure **3.91** in 62% yield. Protection of the secondary alcohol as a PMB-ether (83%) was followed by chemoselective hydroboration with 9-BBN to give alcohol **3.93** in 86% yield. Thioetherification then formed phenylsulfide **3.94** in 87% yield, and subsequent Trost-Curran oxidation gave sulfone **3.95** (76%).

Scheme 3.27 Synthesis of phenylsulfone **3.95**

The  $\alpha$ -lithiated anion of sulfone **3.95** was then added to aldehyde **3.5**, ample supplies of which were available from the previous A83586C studies, to give a mixture of diastereomeric  $\beta$ -hydroxy sulfones **3.96** (Scheme 3.28). This material was oxidized and desulfonated to obtain ketone **3.98** as a single stereoisomer in 71% yield for the 3 steps. Chemoselective removal of the C(34) PMB protecting group and subsequent acid catalysed dehydrative ring-closure provided glycal **3.100** in 91% yield over 2 steps. Cleavage of the C(38) TBS-ether with TBAF in DMF furnished **3.101** (76%) and the methyl ester was replaced with a hydroxybenzotriazole ester group in a two-step procedure to give **3.103** in 72% yield.

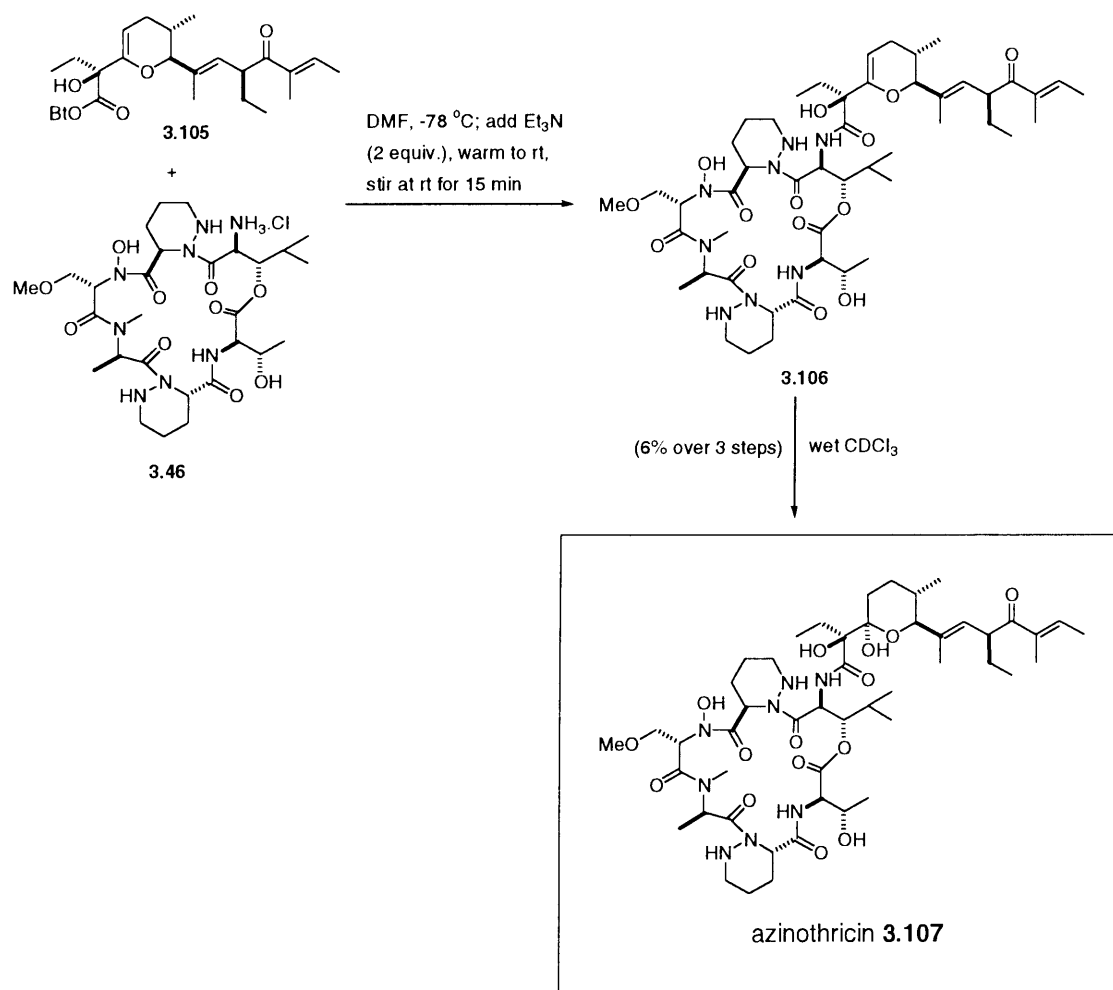


**Scheme 3.28** Synthesis of activated ester **3.105**

Finally, oxidation of the secondary alcohol to a ketone under Swern conditions (73%) and removal of the remaining PMB group with DDQ in wet  $\text{CDCl}_3$  (72%) provided the azinothricin

acyl side chain **3.105** as an activated ester amenable to coupling with suitable cyclodepsipeptide salts.

With the activated ester of the azinothricin acyl side chain in hand, an attempt was made to unify it with the azinothricin cyclodepsipeptide salt **3.46** which had recently been prepared in the Hale group. Accordingly, the two compounds were mixed, and anhydrous DMF was added at  $-78^{\circ}\text{C}$ . Then 2 equiv. of  $\text{Et}_3\text{N}$  were added, and the reaction mixture was allowed to gradually warm to room temperature (Scheme 3.29).



**Scheme 3.29** Total synthesis of azinothricin **3.107**

However, the coupled product was obtained in a very disappointing yield of 6% after several purification steps. After re-examination of the spectral data for **3.46**, we now believe that the

azinothricin cyclodepsipeptide salt had been synthesized in an insufficiently pure form to partake in a coupling reaction with any great efficiency. As such, it is necessary to reinvestigate and repeat the synthesis of **3.46**. On a positive note, the coupled material **3.106** that was obtained underwent a facile hydration in wet  $\text{CDCl}_3$  to give azinothricin **3.107**, as shown by correlation of the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra with the data reported by Maehr<sup>3</sup> and colleagues at Hoffman-La Roche in the original isolation paper.

C No.	Natural azinothricin	Synthetic azinothricin	C No.	Natural azinothricin	Synthetic azinothricin
1	170.35	170.36	26	14.79	14.76
2	56.28	56.27	27	29.43	29.43
3	169.11	169.59	28	175.32	175.32
4	52.43	52.45	29	80.17	80.14
5	24.46	24.46	30	99.67	99.64
6	21.38	21.37	31	28.38	28.37
7	48.05	48.03	32	27.34	27.34
8	173.17	173.18	33	32.45	32.45
9	47.73	47.73	34	82.55	82.56
10	171.09	171.09	35	133.80	133.77
11	53.85	53.86	36	128.56	128.53
12	172.89	172.86	37	45.27	45.27
13	51.33	51.33	38	207.44?	202.69
14	24.16	24.14	39	133.80	138.52
15	21.19	21.18	40	136.79	136.76
16	45.71	45.68	41	14.96	14.94
17	170.92	170.90	42	26.04	26.02
18	54.70	54.70	43	8.33	8.33
19	78.71	78.69	44	17.77	17.76
20	64.85	64.83	45	12.26	12.24
21	18.95	18.94	46	27.83	27.81
22	13.22	13.20	47	11.95	11.93
23	68.57	68.56	48	11.41	11.39
24	29.70	29.68	49	59.25	59.24
25	19.29	19.29			

**Table 3.2** Comparison of the  $^{13}\text{C}$  (50 MHz) NMR data in  $\text{CDCl}_3$  for natural azinothricin<sup>3</sup> with the  $^{13}\text{C}$  (125 MHz) NMR data in  $\text{CDCl}_3$  obtained for **3.107**

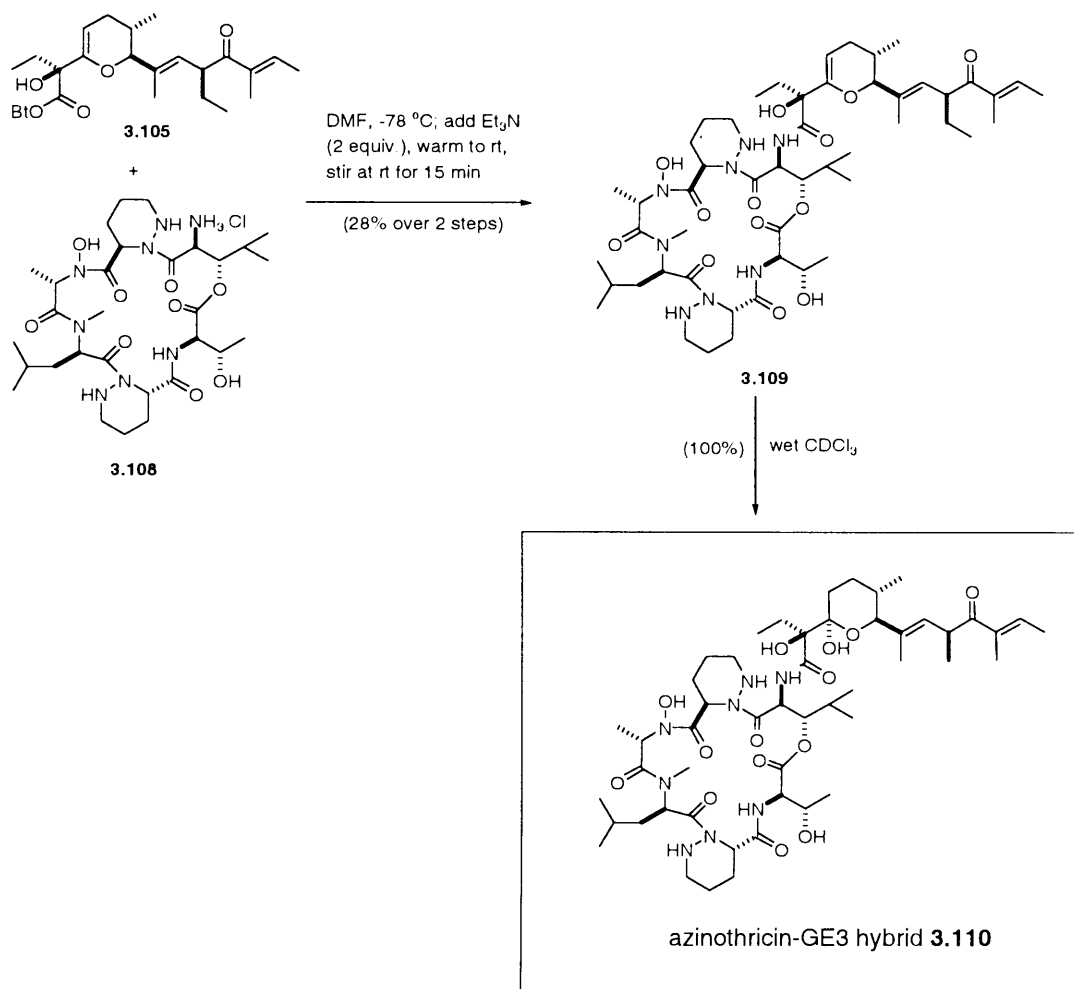
Although the Hoffman-La Roche team only recorded a 200 MHz  $^1\text{H}$  NMR spectrum, a very good agreement between their spectrum and our 500 MHz  $^1\text{H}$  NMR spectrum was evident.

The excellent correlation between the  $^{13}\text{C}$  NMR spectra of synthetic and natural azinothricin was even more conclusive (Table 3.2). The only significant disagreement between our  $^{13}\text{C}$  NMR data and that of Maehr's is the chemical shift of the C-38 carbon atom of the unsaturated ketone, which we report as appearing at 202.69 ppm but which Maehr reports as 207.44 pm. However, our measurement is consistent with the chemical shifts reported for the corresponding carbon atom of A83586C (which appears at 202.93 ppm in  $\text{CDCl}_3$ ), epi-A83586C (203.1 ppm), citropeptin (203.0 ppm) and GE3 (203.1 ppm), as well as the azinothricin activated ester **3.105** (202.8 ppm). We would therefore expect the C-38 chemical shift of azinothricin to be very close to 203 ppm. Given that the Hoffman-La Roche team crystallized azinothricin from acetone, it is probable that they erroneously recorded the chemical shift of the acetone carbonyl group (which appears at 207.07 ppm in  $\text{CDCl}_3$ ) due to residual solvent in their NMR sample, instead of the C-38 carbon atom.

HRMS of the coupled product showed the presence of an  $[\text{M}+\text{Na}]^+$  ion at  $m/e$  1043.5604 which confirmed the empirical formula  $\text{C}_{49}\text{H}_{80}\text{N}_8\text{O}_{15}$  of azinothricin.

The quality of the azinothricin activated ester **3.105** was confirmed by its coupling with the GE3 cyclodepsipeptide salt **3.108** to give another hybrid structure, the azinothricin-GE3 hybrid **3.110** (Scheme 3.30), in a final sequence of reactions that proceeded in a healthier yield of 28% over 3 steps.



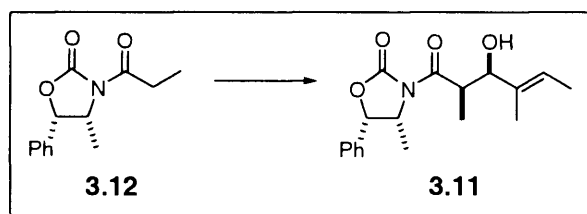


**Scheme 3.30** Synthesis of azinothricin-GE3 hybrid **3.110**

## Conclusion

This thesis has described a new second generation synthetic route to the acyl side chain segment of the A83586C-azinothricin class of cyclodepsipeptide-containing natural products. The optimized route was used to synthesize significant quantities of these acyl side chains in the form of activated benzotriazole esters, which were then coupled with the hydrochloride salts of various cyclodepsipeptides in a biomimetic strategy that avoided the use of protecting groups. This resulted in the first total synthesis of azinothricin and kettapeptin. An A83586C-citropeptin hybrid and an azinothricin-GE3 hybrid were also made by this strategy, and the biological properties of these new molecules will be examined in the future.

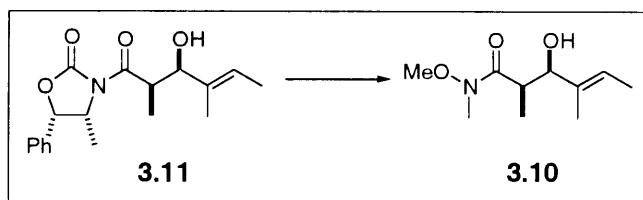
## Chapter 4 Experimental

Aldol adduct **3.11**

To a cooled ( $-10\text{ }^{\circ}\text{C}$  -  $0\text{ }^{\circ}\text{C}$ ) and stirred solution of **3.12** (22.0 g, 94.31 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (300 mL) under  $\text{N}_2$  was successively added  $n\text{-Bu}_2\text{BOTf}$  (1 M solution in  $\text{CH}_2\text{Cl}_2$ , 105.4 mL, 105.4 mmol) dropwise over 1 h, followed by  $\text{Et}_3\text{N}$  (16.5 mL, 118.4 mmol) over 20 min. The internal reaction temperature was maintained below  $0\text{ }^{\circ}\text{C}$  during both additions. Stirring was continued for a further 45 min before the reaction mixture was cooled to  $-78\text{ }^{\circ}\text{C}$  and a solution of tiglic aldehyde (9.98 mL, 103.34 mmol) in  $\text{CH}_2\text{Cl}_2$  (100 mL) was added dropwise over 1 h. The reaction mixture was stirred at  $-78\text{ }^{\circ}\text{C}$  for a further 2 h before warming to rt and pouring into a 10% aq.  $\text{NaH}_2\text{PO}_4$  solution (300 mL). The organic phase was separated and the aqueous phase was extracted with  $\text{Et}_2\text{O}$  (3 x 400 mL). The combined organic extracts were concentrated *in vacuo*, taken up in MeOH (400 mL), and cooled to  $0\text{ }^{\circ}\text{C}$ . A solution of 30% aq.  $\text{H}_2\text{O}_2$  and pH 7 aq. phosphate buffer (1:1, 200 mL) was added dropwise over 15 min to this mixture, and stirring was continued for a further 1 h at  $0\text{ }^{\circ}\text{C}$  until the brown colouration had been discharged. Excess peroxides were quenched with aq.  $\text{FeSO}_4$  and the resulting brown solution was concentrated *in vacuo* to remove excess MeOH. The aqueous residue was extracted with  $\text{Et}_2\text{O}$  (3 x 200 mL), and the combined organic extracts were washed successively with 5% aq.  $\text{NaHCO}_3$  (100 mL) and brine (100 mL) before being dried ( $\text{MgSO}_4$ ), filtered, and concentrated *in vacuo*. Purification of the residue by  $\text{SiO}_2$  flash chromatography (gradient elution using 20:1-10:1-5:1 petrol/ $\text{EtOAc}$  as eluent) and crystallisation ( $\text{Et}_2\text{O}$ /hexanes) of the resultant yellow oil gave 26.7 g (89%) of the desired aldol adduct **3.11** as a white crystalline solid. Data for **3.11**:  $[\alpha]_{\text{D}} +25.5^{\circ}$  ( $c$  0.46,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.43-7.33 (3H, m, Ph), 7.31-7.26 (m, 2H, Ph), 5.65 (1H, d,  $J = 7.2\text{ Hz}$ ,  $\text{PhCH}(\text{O})\text{CH}$ ),

5.61 (1H, dq,  $J = 1.3, 6.7$  Hz,  $\text{CH}_3\text{CH}=\text{C}(\text{CH}_3)-$ ) 4.75 (1H, apparent qn,  $\text{NCH}(\text{CH}_3)\text{CH}(\text{O})-$ ), 4.34 (1H, apparent br s,  $-(\text{HO})\text{CHCH}(\text{CH}_3)-$ ), 3.96 (qd, 1H,  $J = 3.8, 7.0$  Hz,  $-(\text{CH}_3)\text{CHCH}(\text{OH})$ ), 1.63 (3H, d,  $J = 6.8$  Hz,  $\text{CH}_3\text{CH}=\text{C}(\text{CH}_3)-$ ), 1.61 (3H, s,  $\text{CH}_3\text{CH}=\text{C}(\text{CH}_3)-$ ), 1.14 (3H, d,  $J = 7.0$  Hz,  $-(\text{CH}_3)\text{CH}(\text{C}=\text{O})-$ ), 0.87 (3H, d,  $J = 6.6$  Hz,  $-(\text{CH}_3)\text{CH}(\text{N})$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ , 298K):  $\delta$  176.8, 152.6, 134.2, 133.1, 128.8, 128.7, 125.6, 120.5, 78.9, 75.5, 54.9, 40.6, 14.3, 13.1, 13.0, 10.4.

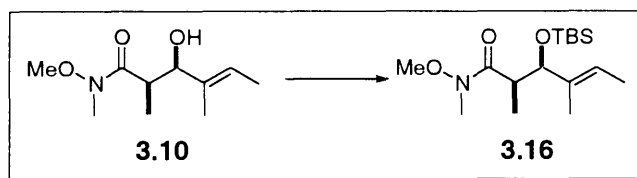
### Weinreb amide **3.10**



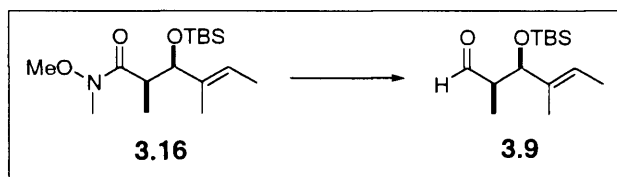
To a suspension of  $\text{MeNHOMe.HCl}$  (9.69 g, 99.34 mmol) in dry THF (80 mL) under  $\text{N}_2$  at  $0^\circ\text{C}$  was cautiously added  $\text{Me}_3\text{Al}$  (2 M solution in hexanes, 50 mL, 100 mmol) dropwise over 0.5 h. The reaction mixture was stirred at  $0^\circ\text{C}$  for 30 min and at rt for 1.5 h before re-cooling to  $-20^\circ\text{C}$ . A pre-cooled solution of **3.11** (10.5 g, 33.1 mmol) in THF (80 mL, 10 mL rinse) was then added via cannula and the reactants were stirred at  $-20^\circ\text{C}$  for 1.5 h. The reaction mixture was quenched by pouring it into a cooled ( $0^\circ\text{C}$ ) solution of aq. HCl (1 M, 200 mL) and  $\text{CH}_2\text{Cl}_2$  (200 mL), and the resultant biphasic mixture was stirred vigorously for 1.5 h at  $0^\circ\text{C}$ . The organic phase was separated and the aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 200 mL). The combined organic extracts were washed with  $\text{H}_2\text{O}$  (100 mL) and brine (100 mL), dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo*. The cleaved oxazolidinone was recovered by crystallisation ( $\text{Et}_2\text{O}$ /hexanes) from the resultant oil. The crude residue that remained was purified by  $\text{SiO}_2$  flash chromatography (gradient elution using 10:1-5:1 petrol/ $\text{EtOAc}$  as eluent) to give the desired product **3.10** (5.54 g, 83%) as a clear colourless oil which eventually crystallized as a white solid after standing. Data for **3.10**:  $[\alpha]_{\text{D}} -16.3^\circ$  ( $c$  0.96,  $\text{CH}_2\text{Cl}_2$ ); IR (KBr)  $\text{cm}^{-1}$ : 3404 (br), 2931 (s), 1636 (s), 1429 (s), 1385 (s), 1312 (m), 1178 (m), 1094 (m), 1034 (m), 986 (m), 831 (m);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ , 298K):  $\delta$  5.62 (1H, dq,  $J = 1.3, 6.8$  Hz,

$\text{CH}_3\text{CH}=\text{C}(\text{CH}_3)$ ), 4.23 (1H, br s,  $(\text{HO})\text{CHCH}(\text{CH}_3)$ ), 3.82-3.62 (1H, br s,  $\text{OH}$ ), 3.68 (3H, s,  $\text{NOCH}_3$ ), 3.17 (3H, s,  $\text{NCH}_3$ ), 3.04 (1H, br s,  $(\text{Me})\text{CHCH}(\text{OH})$ ), 1.60 (3H, d,  $J = 6.8$  Hz,  $\text{CH}_3\text{CH}=\text{C}(\text{CH}_3)$ ), 1.56 (3H, s,  $\text{CH}_3\text{CH}=\text{C}(\text{CH}_3)$ ), 1.06 (3H, d,  $J = 7.1$  Hz,  $(\text{CH}_3)\text{CHC}=\text{O}(\text{NCH}_3)(\text{OCH}_3)$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ , 298K):  $\delta$  178.1, 133.6, 120.4, 75.4, 61.5, 36.9, 31.9, 13.3, 13.0, 10.3; HRMS (FAB+) for  $\text{C}_{10}\text{H}_{19}\text{NNaO}_3$  ( $\text{M}+\text{Na}$ ) $^+$ : Calcd. 224.12626, Found: 224.12593.

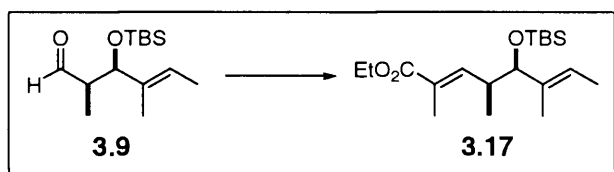
### *tert*-Butyldimethylsilyl Weinreb amide **3.16**



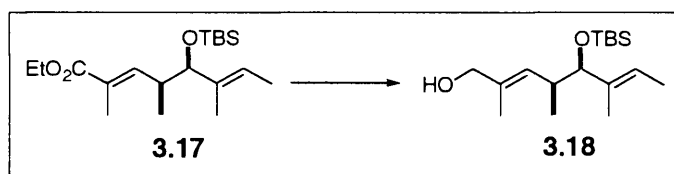
To a solution of **3.10** (21.2 g, 105.3 mmol) in dry DMF (400 mL) at rt under  $\text{N}_2$  were added TBSCl (31.8 g, 211.0 mmol) and imidazole (10.8 g, 158.6 mmol) successively in single portions. The reaction mixture was stirred at rt for 12 h before  $\text{Et}_2\text{O}$  (300 mL) and sat. aq.  $\text{NaHCO}_3$  solution (100 mL) were added. The organic layer was separated, and the aqueous phase was extracted with  $\text{Et}_2\text{O}$  (2 x 300 mL). The combined organic layers were washed with  $\text{H}_2\text{O}$  (500 mL) and brine (200 mL), dried ( $\text{MgSO}_4$ ), filtered, and concentrated *in vacuo*. The crude residue was purified by  $\text{SiO}_2$  flash chromatography (gradient elution using 20:1-10:1 hexanes/ $\text{EtOAc}$ ) to obtain the desired product **3.16** (32.3 g, 97%) as a clear colourless oil. Data for **3.16**:  $[\alpha]_{\text{D}}^{+0.5}$  (c 0.95,  $\text{CH}_2\text{Cl}_2$ ); IR (neat): 2959 (s), 2932 (s), 2858 (m), 1666 (s), 1464 (m), 1379 (m), 1258 (m), 1094 (m), 1057 (s), 997 (m), 876 (s), 837 (s), 775 (s);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  5.35 (1H, q,  $J = 6.6$  Hz,  $\text{CH}_3\text{CH}=\text{C}(\text{CH}_3)$ -), 4.09 (1H, d,  $J = 9.1$  Hz,  $\text{CHCH}_2\text{O}$ ), 3.61 (3H, s,  $\text{NOCH}_3$ ), 3.10 (1H, br s,  $-(\text{CH}_3)\text{CHC}=\text{O}(\text{NMe})(\text{OMe})$ ), 3.07 (3H, s,  $\text{NCH}_3$ ), 1.54 (3H, s,  $\text{CH}_3\text{CH}=\text{C}(\text{CH}_3)$ -), 1.50 (3H, d,  $J = 6.7$  Hz,  $\text{CH}_3\text{CH}=\text{C}(\text{CH}_3)$ -), 1.15 (3H, d,  $J = 6.8$  Hz,  $-(\text{CH}_3)\text{CHC}=\text{O}(\text{NMe})(\text{OMe})$ ), 0.86 (9H, s,  $\text{SiC}(\text{CH}_3)_3$ ), 0.02 (3H, s,  $\text{SiCH}_3$ ), -0.06 (3H, s,  $\text{SiCH}_3$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ , 298K):  $\delta$  176.2, 136.3, 121.6, 80.2, 61.5, 40.4, 32.1, 25.8, 18.2, 14.8, 13.0, 11.0, -4.76, -5.10; HRMS (FAB+) Calcd. for  $\text{C}_{16}\text{H}_{33}\text{NNaO}_3\text{Si}$  ( $\text{M}+\text{Na}$ ) $^+$ : 338.21273. Found: 338.21534.

Aldehyde **3.9**

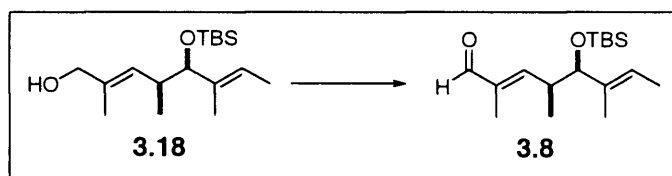
To a solution of **3.16** (7.2 g, 22.82 mmol) in dry PhMe (200 mL) under N<sub>2</sub> at -20 °C was added DIBAL-H (1.5 M solution in PhMe, 15.2 mL, 22.8 mmol) dropwise over 20 min. The reaction mixture was stirred at -20 °C for 10 min before being quenched by the dropwise addition of MeOH (10 mL) over 15 min. A cooled (0 °C) solution of sat. aq. Rochelle's salt (100 mL) and Et<sub>2</sub>O (500 mL) were then added and the mixture was stirred vigorously at rt for 2 h before the organic phase was separated and the aqueous phase further extracted with EtOAc (2 x 200 mL). The combined organic extracts were washed sequentially with sat. aq. Rochelle salt (100 mL), sat. aq. NaHCO<sub>3</sub> (100 mL), and brine (100 mL), dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo*. Purification of the residue by SiO<sub>2</sub> flash chromatography (gradient elution with 100:1-50:1 hexanes/EtOAc as eluent) gave aldehyde **3.9** (4.90 g, 84%) as a runny, colourless liquid. Data for **3.9**: [ $\alpha$ ]<sub>D</sub> +4.8 ° (*c* 1.17, CH<sub>2</sub>Cl<sub>2</sub>); IR (neat) cm<sup>-1</sup>: 2957 (s), 2930 (s), 2858 (m), 1728 (s), 1472 (m), 1388 (w), 1252 (m), 1089 (m), 1058 (s), 837 (s), 775 (s), 673 (w); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  9.62 (1H, d, *J* = 2.0 Hz, (H)C=O), 5.43 (1H, q, *J* = 6.7 Hz, CH<sub>3</sub>CH=C(CH<sub>3</sub>)), 4.22 (1H, d, *J* = 6.3 Hz, (TBSO)CHCH(CH<sub>3</sub>)CHO), 2.49 (1H, m, OHCCCH(CH<sub>3</sub>)CH), 1.57 (3H, d, *J* = 6.8 Hz, CH<sub>3</sub>CH=C(CH<sub>3</sub>)), 1.54 (3H, s, CH<sub>3</sub>C=CH(CH<sub>3</sub>)), 1.01 (3H, d, *J* = 6.9 Hz, (CH<sub>3</sub>)CHCHO), 0.85 (9H, s, SiC(CH<sub>3</sub>)<sub>3</sub>), 0.00 (3H, s, SiCH<sub>3</sub>), -0.05 (3H, s, SiCH<sub>3</sub>); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>, 298K):  $\delta$  204.7, 135.6, 121.8, 78.0, 51.1, 25.7, 18.1, 12.9, 12.0, 9.3, -4.6, -5.3; HRMS (FAB+) Calcd. for C<sub>14</sub>H<sub>28</sub>NaO<sub>2</sub>Si (M+Na)<sup>+</sup>: 279.17562. Found: 279.17298.

$\alpha,\beta$ -Unsaturated ester **3.17**

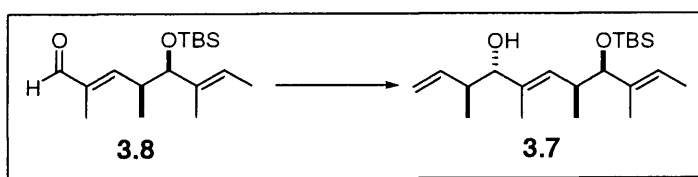
To a solution of aldehyde **3.9** (32.5 g, 126.7 mmol) in anhydrous MeCN (500 mL) under N<sub>2</sub> was added (carbethoxyethylidene)triphenylphosphorane (91.83 g, 253.4 mmol) in four portions. The reaction mixture was heated at 80 °C for 48 h. The reaction mixture was then cooled to rt, and diluted with H<sub>2</sub>O (200 mL) and EtOAc (400 mL). The organic phase was separated, and the aqueous layer was extracted with EtOAc (3 x 300 mL). The combined organics were washed with a saturated aqueous NaHCO<sub>3</sub> solution and brine, dried over MgSO<sub>4</sub> and concentrated *in vacuo* to give an orange slurry. Purification by SiO<sub>2</sub> flash chromatography (gradient elution 100:1 to 20:1 petrol/EtOAc) gave 41.9 g (97%) of **3.17** as a clear, viscous oil. Data for **3.17**: [ $\alpha$ ]<sub>D</sub> +6.1 ° (c 1.0, CH<sub>2</sub>Cl<sub>2</sub>); IR (neat) cm<sup>-1</sup>: 2957 (s), 2931 (s), 2858 (m), 1714 (s), 1651 (w), 1461 (m), 1366 (m), 1253 (m), 1096 (m), 1054 (m), 837 (m), 775 (m); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  6.48 (1H, dd, *J* = 10.3, 1.4 Hz, C=CHCHCH<sub>3</sub>), 5.34 (1H, q, *J* = 6.7 Hz, C=CHCH<sub>3</sub>), 4.14 (2H, m, CH<sub>3</sub>CH<sub>2</sub>O), 3.75 (1H, d, *J* = 7.3 Hz, CHOTBS), 2.59 (1H, m, CH(CH<sub>3</sub>)CHOTBS), 1.79 (3H, d, *J* = 1.4 Hz, CH<sub>3</sub>(CO<sub>2</sub>Et)C=C), 1.52 (3H, d, *J* = 6.6 Hz, CH<sub>3</sub>CH=C), 1.46 (3H, d, *J* = 1.0 Hz, CH<sub>3</sub>C=CHCH<sub>3</sub>), 1.25 (3H, t, *J* = 4.7 Hz, CH<sub>3</sub>CH<sub>2</sub>O), 0.96 (3H, d, *J* = 6.7 Hz, CH<sub>3</sub>CHCHOTBS), 0.87 (9H, s, (CH<sub>3</sub>)<sub>3</sub>C), 0.00 (3H, s, CH<sub>3</sub>Si), -0.07 (3H, s, CH<sub>3</sub>Si); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  168.3 (C-34), 144.9 (C-36), 136.6 (C-35?), 126.2 (C-39?), 121.1 (C-40), 81.7 (C-46), 60.3 (CH<sub>3</sub>CH<sub>2</sub>CO<sub>2</sub>), 38.1 (C-37), 25.8 (CH<sub>3</sub>)<sub>3</sub>CSi, 18.2 (CH<sub>3</sub>)<sub>3</sub>CSi, 15.8 (C-46), 14.2 (CH<sub>3</sub>CH<sub>2</sub>CO<sub>2</sub>), 12.8 (C-41), 12.3 (C-45), 11.4 (C-47), -4.7 (SiCH<sub>3</sub>), -5.3 (SiCH<sub>3</sub>); HRMS (FAB+) Calcd. for C<sub>19</sub>H<sub>28</sub>O<sub>3</sub>SiNa (M+Na)<sup>+</sup>: 363.2359. Found: 363.23375.

Allylic alcohol **3.18**

To a stirred solution of ester **3.17** (41.5 g, 121.9 mmol, azeotroped from benzene) in anhydrous  $\text{CH}_2\text{Cl}_2$  (450 mL) under  $\text{N}_2$  at  $-78^\circ\text{C}$  was added DIBAL-H (1.5 M in toluene, 170.7 mL, 256.0 mmol) dropwise over 40 min. The reaction mixture was stirred at  $-78^\circ\text{C}$  for 2 h before being quenched by careful dropwise addition of MeOH (50 mL). The resultant mixture was poured into a mixture of saturated Rochelle's salt solution (300 mL) and  $\text{Et}_2\text{O}$  (800 mL) at  $0^\circ\text{C}$ . This mixture was stirred at  $0^\circ\text{C}$  for 1 h and at rt for 1 h, at which point a clear separation between the organic and aqueous layers was visible. The organic layer was separated, and the aqueous layer was extracted with  $\text{Et}_2\text{O}$  (2 x 250 mL). The combined organics were washed with brine, dried over  $\text{MgSO}_4$  and concentrated *in vacuo* to give an oil which was used in the next step without further purification. Data for **3.18**:  $[\alpha]_{\text{D}}^{25} +41.7^\circ$  (*c* 1.0,  $\text{CH}_2\text{Cl}_2$ ); IR (neat)  $\text{cm}^{-1}$ : 3323 (s), 2930 (s), 2858 (s), 1462 (s), 1383 (m), 1252 (s), 1084 (s), 874 (s), 773 (s), 671 (m);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  5.24 (1H, q,  $J = 6.7$  Hz,  $\text{C}=\text{CHCH}_3$ ), 5.06 (1H, dd,  $J = 9.8, 1.2$  Hz,  $\text{C}=\text{CHCHCH}_3$ ), 3.86 (2H, s,  $\text{CH}_2\text{OH}$ ), 3.62 (1H, d,  $J = 7.7$  Hz,  $\text{CHOTBS}$ ), 2.47 (1H, m,  $\text{CH}(\text{CH}_3)\text{CHOTBS}$ ), 1.84 (1H, br s, OH), 1.59 (3H, d,  $J = 1.3$  Hz,  $\text{CH}_3(\text{CH}_2\text{OH})\text{C}=\text{C}$ ), 1.49 (3H, d,  $J = 6.7$  Hz,  $\text{CH}_3\text{CH}=\text{C}$ ), 1.45 (3H, s,  $\text{CH}_3\text{C}=\text{CHCH}_3$ ), 0.91 (3H, d,  $J = 6.7$  Hz,  $\text{CH}_3\text{CHCHOTBS}$ ), 0.84 (9H, s,  $(\text{CH}_3)_3\text{C}$ ), -0.03 (3H, s,  $\text{CH}_3\text{Si}$ ), -0.10 (3H, s,  $\text{CH}_3\text{Si}$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  137.3 (C-35/39), 133.4 (C-39/35), 129.6 (C-36), 120.5 (C-40), 82.8 (C-37), 68.9 (C-34), 36.8 (C-38), 25.8 ( $(\text{CH}_3)_3\text{CSi}$ ), 18.2 ( $\text{CH}_3\text{CSi}$ ), 17.1 (C-46), 13.6 (C-45), 12.8 (C-41), 11.3 (C-47), -4.7 ( $\text{SiCH}_3$ ), -5.2 ( $\text{SiCH}_3$ ); HRMS (FAB+) Calcd. for  $\text{C}_{17}\text{H}_{34}\text{O}_2\text{SiNa}$  ( $\text{M}+\text{Na}$ ) $^+$ : 321.22203. Found: 321.22158.

$\alpha,\beta$ -Unsaturated aldehyde **3.8**

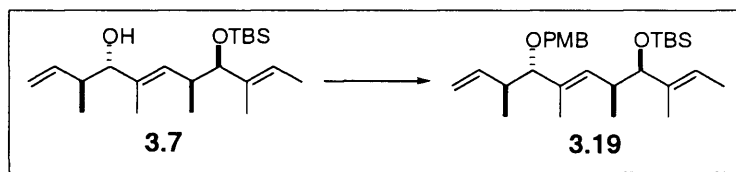
To a stirred solution of allylic alcohol **3.18** (crude, <121.9 mmol) in  $\text{CHCl}_3$  (400 mL) was added  $\text{MnO}_2$  on activated carbon (106.0 g, 1.219 mol). The reaction mixture was refluxed at  $60^\circ\text{C}$  for 24 h, and then cooled to rt and filtered through Celite (filter pad washed with excess  $\text{CH}_2\text{Cl}_2$ ). The filtrate was concentrated *in vacuo* and purified by  $\text{SiO}_2$  flash chromatography (gradient elution 50:1 to 20:1 petrol/EtOAc) to give 30.72 g (85% over 2 steps) of aldehyde **3.8** as a colourless oil. Data for **3.8**:  $[\alpha]_{\text{D}}^{25} +65.0^\circ$  (c 1.15,  $\text{CH}_2\text{Cl}_2$ ); IR (neat)  $\text{cm}^{-1}$ : 2957 (s), 2931 (s), 2857 (s), 1691 (s), 1643 (w), 1460 (m), 1254 (m), 1056 (m), 1017 (m), 863 (m), 835 (s), 775 (m), 674 (w), 567 (w);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.30 (1H, s,  $\text{CHO}$ ), 6.18 (1H, dd,  $J = 10.2, 1.3$  Hz,  $\text{C}=\text{CHCHCH}_3$ ), 5.34 (1H, q,  $J = 6.2$  Hz,  $\text{C}=\text{CHCH}_3$ ), 3.79 (1H, d,  $J = 7.7$  Hz,  $\text{CHOTBS}$ ), 2.81 (1H, m,  $\text{CH}(\text{CH}_3)\text{CHOTBS}$ ), 1.71 (3H, d,  $J = 1.3$  Hz,  $\text{CH}_3(\text{CHO})\text{C}=\text{C}$ ), 1.52 (3H, d,  $J = 6.7$  Hz,  $\text{CH}_3\text{CH}=\text{C}$ ), 1.47 (3H, s,  $\text{CH}_3\text{C}=\text{CHCH}_3$ ), 1.04 (3H, d,  $J = 6.7$  Hz,  $\text{CH}_3\text{CHCHOTBS}$ ), 0.87 (9H, s,  $(\text{CH}_3)_3\text{CSi}$ ), 0.01 (3H, s,  $\text{CH}_3\text{Si}$ ), -0.06 (3H, s,  $\text{CH}_3\text{Si}$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  195.6 (C-34), 157.3 (C-36), 137.8 (C-35/39), 136.7 (C-39/35), 121.6 (C-40), 81.9 (C-37), 38.5 (C-38), 25.8 ( $\text{CH}_3\text{CSi}$ ), 18.2 ( $\text{CH}_3\text{CSi}$ ), 16.1 (C-46), 12.8 (C-41), 11.2 (C-47), 9.1 (C-45), -4.7 ( $\text{SiCH}_3$ ), -5.2 ( $\text{SiCH}_3$ ).

Allylic alcohol **3.7**

180 mL of an approximately 1 M solution of (*R,R*)-diisopropyl tartrate (*E*)-crotylboronate in toluene was prepared according to the procedure of Roush.<sup>67</sup> 101.2 mL (101.2 mmol) of this

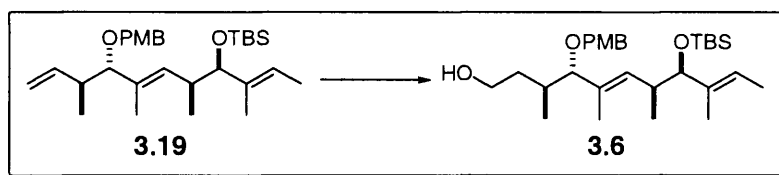


freshly prepared solution was added to a flask containing 350 mL of anhydrous toluene and approximately 10 g of activated 4 Å molecular sieves under N<sub>2</sub> at rt. This mixture was stirred at rt for 30 min, and then cooled to -78 °C. A solution of aldehyde **3.8** (20.0 g, 67.4 mmol) in dry toluene (100 mL) was added dropwise via syringe over 1 h. The reaction mixture was stirred at -78 °C for a further 2 h, and then a further 33.7 mL (33.7 mmol) of the 1 M solution of (*R, R*)-diisopropyl tartrate (*E*)-crotylboronate in toluene was added dropwise over 20 min. The reactants were stirred at -78 °C for a further 1 h, at which point TLC analysis indicated complete conversion of the aldehyde starting material. 130 mL of 2 M NaOH solution was then added to hydrolyse DIPT. The reaction mixture was warmed to rt and stirred for 1 h, and then diluted with Et<sub>2</sub>O (400 mL) and filtered through celite. The organic layer was separated and the aqueous layer was extracted with Et<sub>2</sub>O (3 x 300 mL). The combined organics were washed with brine (300 mL), dried over anhydrous MgSO<sub>4</sub> and filtered. The filtrate was concentrated under reduced pressure and purified by silica gel flash chromatography (gradient elution 100:1 to 50:1 petrol/EtOAc) to give 15.4 g (65%) of product **3.7** as a colourless oil. Data for **3.7**: [ $\alpha$ ]<sub>D</sub> +20.8 ° (c 0.88, CH<sub>2</sub>Cl<sub>2</sub>); IR (neat) cm<sup>-1</sup>: 3475 (m), 2958 (s), 2929 (s), 2857 (s), 1638 (w), 1459 (m), 1383 (m), 1363 (m), 1253 (s), 1085 (s), 1052 (s), 1006 (s), 939 (m), 910 (s), 874 (s), 836 (s), 774 (s), 669 (m), 565 (m); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  5.71 (1H, m, H<sub>2</sub>C=CH), 5.28 (1H, q, *J* = 6.6 Hz, C=CHCH<sub>3</sub>), 5.12-5.07 (3H, m, C=CH<sub>2</sub>, C=CHCHCH<sub>3</sub>), 3.66 (1H, d, *J* = 8.0 Hz, CHOTBS), 3.59 (1H, d, *J* = 7.9 Hz, CHOH), 2.52 (1H, m, CH(CH<sub>3</sub>)CHOTBS), 2.29 (1H, m, CH(CH<sub>3</sub>)CHOH), 1.57 (3H, d, *J* = 1.2 Hz, CH<sub>3</sub>(CHOH)C=C), 1.52 (3H, d, *J* = 6.7 Hz, CH<sub>3</sub>CH=C), 1.47 (3H, s, CH<sub>3</sub>C=CHCH<sub>3</sub>), 0.93 (3H, d, *J* = 6.7 Hz, CH<sub>3</sub>CHCHOTBS), 0.87 (3H, superimposed d, CH<sub>3</sub>CHCHOH), 0.86 (9H, s, (CH<sub>3</sub>)<sub>3</sub>C), 0.0 (3H, s, CH<sub>3</sub>Si), -0.07 (3H, s, CH<sub>3</sub>Si); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  140.9 (C-32?), 137.4 (C-35?), 133.6 (C-39?), 131.2 (C-36), 120.8 (C-40), 115.9 (C-31), 83.1 (C-37), 80.8 (C-34), 41.8 (C-33), 36.9 (C-37), 25.8 (CH<sub>3</sub>)<sub>3</sub>CSi, 18.2 (CH<sub>3</sub>)<sub>3</sub>CSi, 17.2 (C-46), 16.5 (C-44), 12.8 (C-41), 11.8 (C-45), 11.2 (C-47), -4.7 (SiCH<sub>3</sub>), -5.1 (SiCH<sub>3</sub>); HRMS (FAB+) Calcd. for C<sub>21</sub>H<sub>40</sub>O<sub>2</sub>SiNa (M+Na)<sup>+</sup>: 375.26898. Found: 375.26925.

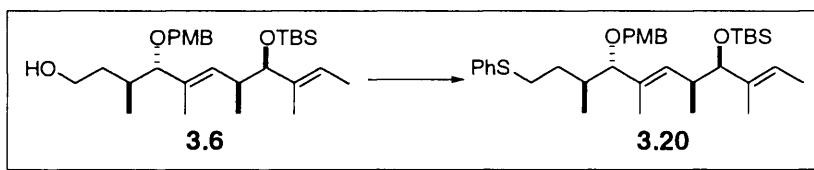
PMB-ether **3.19**

To a solution of alcohol **3.7** (16.00 g, 45.4 mmol) and PMB-acetimidate (38.45 g, 136.1 mmol) in dry Et<sub>2</sub>O (250 mL) at 0 °C under N<sub>2</sub> was added TfOH (0.02 M in Et<sub>2</sub>O, 11.35 mL, 0.23 mmol) dropwise over 10 min. The reaction mixture was stirred at rt for 2 h, then quenched with saturated aqueous NaHCO<sub>3</sub> solution (100 mL) and diluted with Et<sub>2</sub>O (300 mL). The organic layer was separated and the aqueous layer was extracted with Et<sub>2</sub>O (2 x 200 mL). The combined organics were washed with brine, dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. Purification by SiO<sub>2</sub> flash chromatography (gradient elution 100:1 to 50:1 petrol/EtOAc) gave 18.85 g (88%) of PMB-ether **3.19** as a colourless oil. Data for **3.19**: [ $\alpha$ ]<sub>D</sub> +20.4 ° (c 0.82, CH<sub>2</sub>Cl<sub>2</sub>); IR (neat) cm<sup>-1</sup>: 3076 (m), 2930 (s), 2857 (s), 1639 (m), 1613 (s), 1586 (m), 1513 (s), 1460 (s), 1376 (s), 1300 (s), 1249 (s), 1175 (s), 1053 (s), 939 (m), 869 (s), 774 (s), 670 (m), 574 (m), 515 (w); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  7.18 (2H, d, *J* = 8.4 Hz, ArH), 6.84 (2H, d, *J* = 8.4 Hz, ArH), 5.84 (1H, m, H<sub>2</sub>C=CH), 5.34 (1H, q, *J* = 6.2 Hz, C=CHCH<sub>3</sub>), 5.02-4.93 (3H, m, C=CH<sub>2</sub>, C=CHCHCH<sub>3</sub>), 4.28 (1H, d, *J* = 11.6 Hz, OCH<sub>2</sub>Ar), 3.98 (1H, d, *J* = 11.6 Hz, OCH<sub>2</sub>Ar), 3.78 (3H, s, ArOCH<sub>3</sub>), 3.68 (1H, d, *J* = 8.9 Hz, CHOTBS), 3.21 (1H, d, *J* = 7.9 Hz, CHOPMB), 2.64 (1H, m, CH(CH<sub>3</sub>)CHOTBS), 2.35 (1H, m, CH(CH<sub>3</sub>)CHOPMB), 1.56 (3H, s, CH<sub>3</sub>), 1.55 (3H, s, CH<sub>3</sub>), 1.52 (3H, d, *J* = 6.7 Hz, CH<sub>3</sub>CH=C), 0.98 (3H, d, *J* = 6.6 Hz, CH<sub>3</sub>CHCHOTBS), 0.88 (9H, s, (CH<sub>3</sub>)<sub>3</sub>C), 0.77 (3H, d, *J* = 8.9 Hz, CH<sub>3</sub>CHCHOPMB), 0.04 (3H, s, CH<sub>3</sub>Si), -0.03 (3H, s, CH<sub>3</sub>Si); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  158.9, 142.5, 138.1, 133.9, 131.6, 131.1, 129.3, 121.1, 113.6, 113.3, 89.2, 83.9, 68.9, 55.2, 39.6, 37.3, 25.9, 18.2, 18.0, 16.4, 13.0, 10.75, 10.66, -4.6, -5.1; HRMS (FAB+) Calcd. for C<sub>29</sub>H<sub>48</sub>O<sub>3</sub>SiNa (M+Na)<sup>+</sup>: 495.32702. Found: 495.32748.

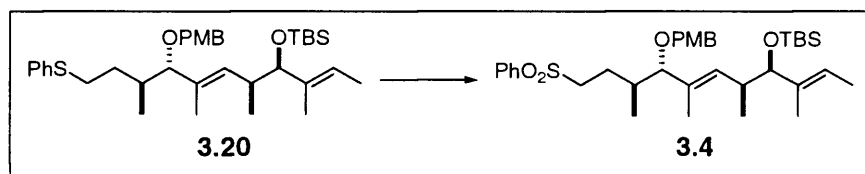
## Alcohol 3.6



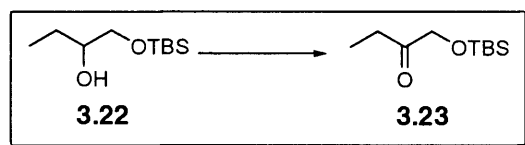
To a solution of PMB-ether **3.19** (13.90 g, 29.4 mmol) in anhydrous THF (300 mL) under N<sub>2</sub> atmosphere at 0 °C was added a 0.5 M solution of 9-BBN in THF (117.6 mL, 58.8 mmol) dropwise over 30 min. The reaction mixture was stirred at 0 °C for 10 min, then allowed to warm to ambient temperature and stirred at rt for 2 h. The reaction mixture was then re-cooled to 0 °C, and a pre-mixed solution of 2M NaOH (80 mL) and 30% H<sub>2</sub>O<sub>2</sub> (80 mL) was carefully added. The resultant mixture was warmed to rt and stirred at this temperature for 2 h. Brine (150 mL) and Et<sub>2</sub>O (300 mL) were added, and the organic layer was separated. The aqueous phase was extracted with Et<sub>2</sub>O (3 x 100 mL), and the combined organics were dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. Purification by SiO<sub>2</sub> flash chromatography (gradient elution 10:1 to 5:1 petrol/EtOAc) gave 11.90 g (83%) of alcohol **3.6** as a clear, viscous oil. Data for **3.6**: [ $\alpha$ ]<sub>D</sub> +12.5° (c 0.69, CH<sub>2</sub>Cl<sub>2</sub>); IR (neat) cm<sup>-1</sup>: 3410 (br s), 2956 (s), 2929 (s), 2857 (s), 1612 (w), 1513 (s), 1463 (m), 1383 (w), 1301 (w), 1249 (s), 1175 (w), 1052 (s), 835 (m), 774 (m), 669 (w); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  7.18 (2H, d, *J* = 8.4 Hz, ArH), 6.84 (2H, d, *J* = 8.4 Hz, ArH), 5.32 (1H, q, *J* = 6.7 Hz, C=CHCH<sub>3</sub>), 5.01 (1H, dd, *J* = 10.0, 1.1 Hz, C=CHCHCH<sub>3</sub>), 4.25 (1H, d, *J* = 11.1 Hz, OCH<sub>2</sub>Ar), 3.96 (1H, d, *J* = 11.1 Hz, OCH<sub>2</sub>Ar), 3.78 (3H, s, ArOCH<sub>3</sub>), 3.67 (1H, d, *J* = 9.0 Hz, CHOTBS), 3.63 (1H, m, CHHOH), 3.54 (1H, m, CHHOH), 3.17 (1H, d, *J* = 9.2 Hz, CHOPMB), 2.62 (2H, m, CH(CH<sub>3</sub>)CHOTBS, CH(CH<sub>3</sub>)CHOPMB), 1.54 (3H, d, *J* = 1.3 Hz, CH<sub>3</sub>), 1.53 (3H, s, CH<sub>3</sub>), 1.46 (3H, dd, *J* = 6.7, 1.0 Hz, CH<sub>3</sub>CH=C), 0.97 (3H, d, *J* = 6.6 Hz, CH<sub>3</sub>CHCHOTBS), 0.87 (9H, s, (CH<sub>3</sub>)<sub>3</sub>C), 0.69 (3H, d, *J* = 6.8 Hz, CH<sub>3</sub>CHCHOPMB), 0.02 (3H, s, CH<sub>3</sub>Si), -0.05 (3H, s, CH<sub>3</sub>Si); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  159.1, 138.1, 134.2, 131.6, 130.3, 129.8, 121.2, 113.7, 90.4, 83.9, 69.1, 55.2, 38.0, 37.3, 33.3, 25.9, 18.2, 18.0, 17.9, 13.0, 10.7, 10.5, -4.6, -5.1; HRMS (FAB+) Calcd. for C<sub>29</sub>H<sub>50</sub>O<sub>4</sub>SiNa (M+Na)<sup>+</sup>: 513.33759. Found: 513.33766.



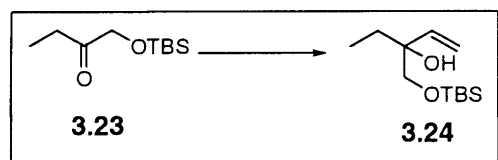
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Phenylsulfone **3.4**

To a stirred solution of thioether **3.20** (3.10 g, 5.32 mmol) in THF/MeOH/H<sub>2</sub>O (1:1:1, 45 mL) was added Oxone<sup>TM</sup> (9.81 g, 15.95 mmol) at rt. The reaction mixture was stirred at rt for 3 h, before dilution with EtOAc (150 mL) and H<sub>2</sub>O (50 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organics were washed with brine, dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. Purification by SiO<sub>2</sub> flash chromatography (gradient elution 10:1 to 6:1 petrol/EtOAc) gave 2.90 g (89%) of phenylsulfone **3.4** as a thick, colourless oil. Data for **3.4**: [ $\alpha$ ]<sub>D</sub> +14.1 ° (*c* 0.50, CH<sub>2</sub>Cl<sub>2</sub>); IR (neat) cm<sup>-1</sup>: 2957 (s), 2930 (s), 2857 (s), 1612 (m), 1585 (w), 1513 (s), 1461 (m), 1448 (m), 1383 (w), 1304 (s), 1250 (s), 1176 (m), 1148 (s), 1086 (s), 1054 (s), 1006 (m), 875 (m), 836 (s), 775 (m), 690 (m), 592 (w), 538 (m); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  7.83-7.80 (2H, m, ArH), 7.62-7.59 (1H, m, ArH), 7.51-7.48 (2H, m, ArH), 7.06 (2H, d, *J* = 8.4 Hz, ArH), 6.82 (2H, d, *J* = 8.3 Hz, ArH), 5.31 (1H, q, *J* = 6.1 Hz, C=CHCH<sub>3</sub>), 4.96 (1H, d, *J* = 10.0 Hz, C=CHCHCH<sub>3</sub>), 4.16 (1H, d, *J* = 11.3 Hz, OCHHAr), 3.86 (1H, d, *J* = 11.3 Hz, OCHHAr), 3.80 (3H, s, ArOCH<sub>3</sub>), 3.65 (1H, d, *J* = 8.9 Hz, CHOTBS), 3.11 (1H, td, *J* = 13.7, 4.6 Hz, PhSO<sub>2</sub>CHHCH<sub>2</sub>), 3.04 (1H, d, *J* = 9.6 Hz, CHOPMB), 2.98 (1H, td, *J* = 13.7, 4.6 Hz, PhSO<sub>2</sub>CHHCH<sub>2</sub>), 2.59 (1H, m, CH(CH<sub>3</sub>)CHOTBS), 1.93 (1H, m, PhSO<sub>2</sub>CH<sub>2</sub>CHH), 1.64 (1H, m, CH(CH<sub>3</sub>)CHOPMB), 1.56 (1H, m, PhSO<sub>2</sub>CH<sub>2</sub>CHH), 1.52 (3H, s, CH<sub>3</sub>), 1.48-1.46 (6H, m, CH<sub>3</sub>, CH<sub>3</sub>CH=C), 0.94 (3H, d, *J* = 6.6 Hz, CH<sub>3</sub>CHCHOTBS), 0.86 (9H, s, (CH<sub>3</sub>)<sub>3</sub>C), 0.62 (3H, d, *J* = 6.8 Hz, CH<sub>3</sub>CHCHOPMB), 0.02 (3H, s, CH<sub>3</sub>Si), -0.06 (3H, s, CH<sub>3</sub>Si); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  159.0, 139.2, 138.1, 134.5, 133.4, 131.2, 130.5, 129.6, 129.1, 128.1, 121.2, 113.7, 89.2, 83.8, 68.8, 55.2, 54.3, 37.3, 33.8, 26.7, 25.8, 18.2, 17.9, 16.2, 13.0, 10.7, 10.3, -4.6, -5.1; HRMS (FAB+) Calcd. for C<sub>35</sub>H<sub>54</sub>O<sub>5</sub>SSiNa (M+Na)<sup>+</sup>: 637.33587. Found: 637.33437.

**Ketone 3.23**

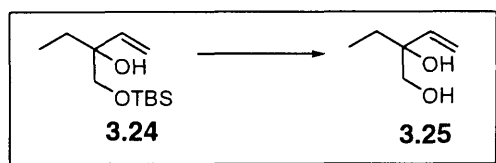
To a solution of alcohol **3.22** (<111.0 mmol) in H<sub>2</sub>O (150 mL) / CCl<sub>4</sub> (100 mL) / MeCN (100 mL) was added RuCl<sub>3</sub>·xH<sub>2</sub>O (0.48 g, 2.31 mmol) and NaIO<sub>4</sub> (49.3 g, 230.6 mmol) in 2 portions at 0 °C. The reaction mixture was stirred at 0 °C for 30 min, then warmed to rt and stirred at rt for a further 1.5 h. The mixture was then diluted with H<sub>2</sub>O (300 mL) and CH<sub>2</sub>Cl<sub>2</sub> (300 mL). The organic layer was separated, and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 300mL). The combined organics were washed with brine, dried over MgSO<sub>4</sub> and concentrated under reduced pressure. Purification by SiO<sub>2</sub> flash chromatography (gradient elution 20:1 to 10:1 petrol/EtOAc) gave 17.0 g (77% for 2 steps) of ketone **3.23** as a clear oil. Data for **3.23**: IR (neat) cm<sup>-1</sup>: 3431 (br s), 2931 (s), 2886 (s), 2858 (s), 1721 (s), 1463 (m), 1362 (w), 1257 (s), 1174 (w), 1109 (s), 839 (s), 779 (s), 668 (w); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 4.09 (2H, s, CH<sub>2</sub>OTBS), 2.45 (2H, q, *J* = 7.3 Hz, CH<sub>2</sub>CH<sub>3</sub>), 0.98 (3H, t, *J* = 7.3 Hz, CH<sub>2</sub>CH<sub>3</sub>), 0.85 (9H, s, (CH<sub>3</sub>)<sub>3</sub>C), 0.00 (6H, s, CH<sub>3</sub>Si); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 211.5, 69.0, 31.5, 25.6, 18.1, 7.1, -5.7.

**Alcohol 3.24**

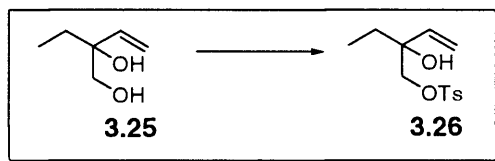
To a solution of ketone **3.23** (20.0 g, 98.8 mmol) in anhydrous THF (300 mL) at 0 °C under N<sub>2</sub> was added vinylmagnesium bromide (1.0 M in THF, 138.4 mL, 138.4 mmol) over 20 min. The reaction mixture was stirred at 0 °C for 1 h, then warmed to rt and stirred at rt for 30 min. The reaction mixture was then quenched with saturated aqueous NH<sub>4</sub>Cl solution (150 mL) and

diluted with Et<sub>2</sub>O. The organic layer was then separated and the aqueous phase extracted with Et<sub>2</sub>O (3 x 100 mL). The combined organics were washed with brine, dried over MgSO<sub>4</sub> and conc. *in vacuo*. **3.24** was then taken on to the next step without further purification. Data for **3.24**: IR (neat) cm<sup>-1</sup>: 3473 (br m), 2932 (s), 2858 (s), 1468 (m), 1256 (s), 1100 (s), 920 (m), 839 (s), 778 (s), 669 (w); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 5.72 (1H, dd, *J* = 17.4, 10.9 Hz, HHC=CH), 5.26 (1H, dd, *J* = 17.4, 1.6 Hz, HHC=CH), 5.13 (1H, dd, *J* = 10.9, 1.5 Hz, H<sub>2</sub>C=CH), 3.44 (2H, s, CH<sub>2</sub>OTBS), 2.40 (1H, s, OH), 1.61-1.54 (1H, m, CHHCH<sub>3</sub>), 1.48-1.40 (1H, m, CHHCH<sub>3</sub>), 0.86 (9H, s, (CH<sub>3</sub>)<sub>3</sub>C), 0.84 (3H, t, *J* = 7.5 Hz, CH<sub>2</sub>CH<sub>3</sub>), 0.02 (3H, s, CH<sub>3</sub>Si), 0.00 (3H, s, CH<sub>3</sub>Si); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 140.8, 114.3, 75.4, 69.2, 29.6, 25.8, 18.3, 7.6, -5.45, -5.52. HRMS (FAB+) Calcd. for C<sub>12</sub>H<sub>26</sub>O<sub>2</sub>SiNa (M+Na)<sup>+</sup>: 253.15997. Found: 253.15941.

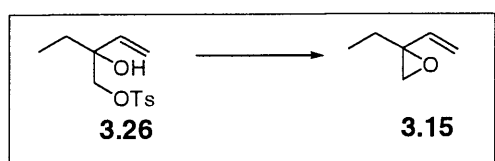
### Diol **3.25**



To a solution of crude alcohol **3.24** (<98.8 mmol) in THF (250 mL) at rt was added aq. HCl (1.0 M, 118.6 mL, 118.6 mmol). The reaction mixture was stirred at rt for 4 h, then quenched with aq. NaHCO<sub>3</sub> solution and diluted with EtOAc (300 mL) and H<sub>2</sub>O (300 mL). The organic layer was washed with brine, dried over MgSO<sub>4</sub> and concentrated under reduced pressure to give diol **3.25**, which was taken on without further purification. Data for **3.25**: IR (neat) cm<sup>-1</sup>: 3384 (br s), 2971 (s), 2936 (s), 2881 (m), 1645 (w), 1460 (w), 1381 (w), 1272 (w), 1181 (w), 1050 (s), 993 (m), 924 (m), 675 (w); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 5.74 (1H, dd, *J* = 17.4, 10.9 Hz, HHC=CH), 5.30 (1H, dd, *J* = 17.4, 1.3 Hz, HHC=CH), 5.22 (1H, dd, *J* = 10.9, 1.3 Hz, H<sub>2</sub>C=CH), 3.46 (2H, m, CH<sub>2</sub>OH), 2.54 (1H, s, OH), 2.45 (1H, s, OH), 1.61-1.45 (2H, m, CH<sub>2</sub>CH<sub>3</sub>), 0.85 (3H, t, *J* = 7.5 Hz, CH<sub>2</sub>CH<sub>3</sub>); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 140.4, 115.2, 76.2, 68.4, 29.5, 7.4. HRMS (CI) Calcd. for C<sub>6</sub>H<sub>13</sub>O<sub>2</sub> (M+H)<sup>+</sup>: 117.09155. Found: 117.09099.

Tosylate **3.26**

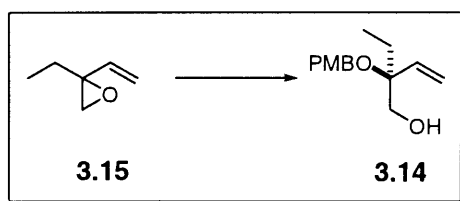
To a solution of crude diol **3.25** (<98.8 mmol) in anhydrous pyridine (150 mL) was added TsCl (18.4 g, 96.4 mmol) at 0 °C under N<sub>2</sub>. The reaction mixture was stirred at 0 °C for 1 h, then warmed to rt and stirred for 4 h. The reaction mixture was then quenched by addition of H<sub>2</sub>O (100 mL) and extracted with Et<sub>2</sub>O (3 x 150 mL). The combined organic extracts were then washed sequentially with 10% aq. H<sub>2</sub>SO<sub>4</sub> (150 mL), brine (150 mL) and sat. aq. NaHCO<sub>3</sub> solution (150 mL). The organic extracts were then dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The crude material was azeotroped from toluene to remove excess pyridine before purification by SiO<sub>2</sub> flash chromatography (10:1 to 5:1 petrol/EtOAc as eluent) to give 21.10 g of tosylate **3.26** as an oil in 79% yield over 3 steps. Data for **3.26**: IR (neat) cm<sup>-1</sup>: 3527 (br m), 2974 (m), 2941 (m), 1734 (w), 1598 (m), 1456 (m), 1360 (s), 1177 (s), 1097 (m), 977 (s), 951 (s), 840 (s), 815 (s), 667 (s), 556 (s); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.73 (2H, d, *J* = 8.3 Hz, ArH), 7.29 (2H, d, *J* = 8.0 Hz, ArH), 5.64 (1H, dd, *J* = 17.3, 10.9 Hz, HHC=CH), 5.25 (1H, dd, *J* = 17.3, 1.1 Hz, HHC=CH), 5.15 (1H, dd, *J* = 10.9, 1.0 Hz, H<sub>2</sub>C=CH), 3.85 (2H, s, CH<sub>2</sub>OTs), 2.39 (3H, s, ArCH<sub>3</sub>), 2.23 (1H, s, OH), 1.59-1.52 (1H, m, CHHCH<sub>3</sub>), 1.49-1.41 (1H, m, CHHCH<sub>3</sub>), 0.77 (3H, t, *J* = 7.5 Hz); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 144.9, 138.4, 132.4, 129.8, 127.8, 115.8, 74.8, 74.1, 29.5, 21.5, 7.0; HRMS (FAB+) Calcd. for C<sub>13</sub>H<sub>18</sub>O<sub>4</sub>SNa (M+Na)<sup>+</sup>: 293.08234. Found: 293.08162.

Epoxide **3.15**



To a solution of tosylate **3.26** (66.0 g, 244.1 mmol) in Et<sub>2</sub>O (600 mL) under N<sub>2</sub> at 0 °C was added finely ground KOH (27.40 g, 488.2 mmol) in 3 portions over 10 min. The reaction mixture was stirred at 0 °C for 30 min, then warmed to rt and stirred for a further 30 min. The reaction was accompanied by formation of a thick white precipitate. The mixture was filtered through Celite, with the filter cake washed with Et<sub>2</sub>O. Distillation of the filtrate at atmospheric pressure gave pure vinyl epoxide **3.15** (20.9 g, 87%, b.p. = 96-98 °C) as a clear liquid. Data for **3.15**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 5.73 (1H, dd, *J* = 17.4, 10.8 Hz, HH<sub>C</sub>=CH), 5.32 (1H, dd, *J* = 17.4, 1.2 Hz, HH<sub>C</sub>=CH), 5.20 (1H, dd, *J* = 10.8, 1.2 Hz, H<sub>2</sub>C=CH), 2.79 (1H, d, *J* = 5.3 Hz, CHHO), 2.65 (1H, d, *J* = 5.3 Hz, CHHO), 1.80-1.67 (2H, m, CH<sub>2</sub>CH<sub>3</sub>), 0.95 (3H, t, *J* = 7.5 Hz, CH<sub>2</sub>CH<sub>3</sub>); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 137.4, 116.5, 59.3, 54.6, 26.1, 9.1.

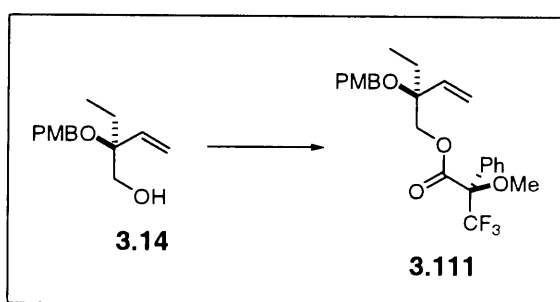
#### Alcohol **3.14**



Degassed, anhydrous CH<sub>2</sub>Cl<sub>2</sub> (700 mL) was added to a flask containing PMB-OH (14.68 g, 106.3 mmol), (*R,R*) Trost chiral amide ligand (2.01 g, 2.91 mmol) and (dba)<sub>3</sub>Pd<sub>2</sub>.CHCl<sub>3</sub> (1.00 g, 0.97 mmol) at rt under N<sub>2</sub>. The resultant dark purple solution was stirred at rt for 5 min until a dark brown/orange colour appeared. The Et<sub>3</sub>B (1 M in THF, 0.97 mL, 0.97 mmol) was added dropwise, followed by epoxide **3.15** (9.48 g, 96.6 mmol) in one portion. The resultant pale yellow/olive solution was stirred at rt for 36 h. The reaction mixture was then concentrated *in vacuo* and purified by SiO<sub>2</sub> flash chromatography (4:1 petrol/EtOAc as eluent) to give 16.90 g (74%) of alcohol **3.14** as a colourless oil. Data for **3.14**: [α]<sub>D</sub> -2.6 ° (*c* 1.73, CH<sub>2</sub>Cl<sub>2</sub>); IR (neat) cm<sup>-1</sup>: 3442 (s), 2968 (s), 2936 (s), 2836 (m), 1613 (s), 1514 (s), 1464 (s), 1380 (m), 1301 (m), 1249 (s), 1174 (m), 1037 (s), 929 (m), 823 (m); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.25 (2H, d, *J* = 8.6 Hz, ArH), 6.86 (2H, d, *J* = 8.6 Hz, ArH), 5.83 (1H, dd, *J* = 17.8, 11.2 Hz, HH<sub>C</sub>=CH), 5.35 (1H, dd, *J* = 11.1, 1.2 Hz, H<sub>2</sub>C=CH), 5.28 (1H, dd, *J* = 17.8, 1.2 Hz,

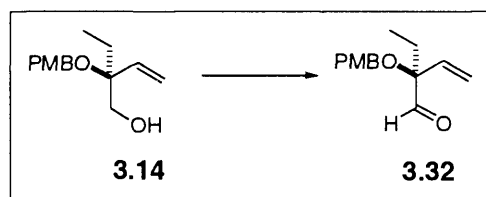
HHC=CH), 4.33 (2H, m, OCH<sub>2</sub>Ar), 3.78 (3H, s, ArOCH<sub>3</sub>), 3.64 (1H, d,  $J$  = 11.4 Hz, CHHOH), 3.58 (1H, d,  $J$  = 11.4 Hz, CHHOH), 1.79 (1H, br s, CH<sub>2</sub>OH), 1.73 (2H, qd,  $J$  = 7.5, 2.3 Hz, CH<sub>2</sub>CH<sub>3</sub>), 0.91 (3H, t,  $J$  = 7.5 Hz, CH<sub>2</sub>CH<sub>3</sub>); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 158.6, 138.4, 130.6, 128.5, 116.7, 113.4, 79.8, 64.2, 63.4, 54.8, 25.1, 7.2; HRMS (FAB+) Calcd. for C<sub>14</sub>H<sub>20</sub>O<sub>3</sub>Na (M+Na)<sup>+</sup>: 259.13101. Found: 259.11048.

### Mosher ester **3.111**



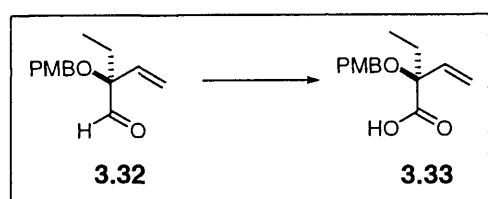
To a solution of alcohol **3.14** in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (4 mL) was added (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid ((+)-Mosher's acid, 108 mg, 0.46 mmol), DCC (173 mg, 0.84 mmol) and DMAP (5.2 mg, 0.042 mmol). The reaction mixture was stirred at rt for 2 h, at which point the reaction was complete by TLC. The mixture was then diluted with CH<sub>2</sub>Cl<sub>2</sub>, filtered to remove the urea by-product, washed with water and dried over MgSO<sub>4</sub>. The solution was concentrated *in vacuo* and purified by SiO<sub>2</sub> flash chromatography (8:1 petrol/EtOAc as eluent) to give 180 mg (95%) of ester **3.111** as a clear oil. <sup>19</sup>F NMR of the product shows effectively one diastereoisomer. Data for **3.111**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.52 (2H, d,  $J$  = 7.6 Hz, ArH), 7.44-7.29 (3H, m, ArH), 7.18 (2H, d,  $J$  = 8.6 Hz, ArH), 6.83 (2H, d,  $J$  = 8.6 Hz, ArH), 5.80 (1H, dd,  $J$  = 17.8, 11.2 Hz, HHC=CH), 5.32 (1H, dd,  $J$  = 11.1, 1.2 Hz, H<sub>2</sub>C=CH), 5.27 (1H, dd,  $J$  = 17.8, 1.2 Hz, HHC=CH), 4.42 (2H, s, CH<sub>2</sub>OC(O)), 4.30 (2H, m, OCH<sub>2</sub>Ar), 3.78 (3H, s, ArOCH<sub>3</sub>), 1.72 (2H, qd,  $J$  = 7.5, 2.3 Hz, CH<sub>2</sub>CH<sub>3</sub>), 0.90 (3H, t,  $J$  = 7.5 Hz, CH<sub>2</sub>CH<sub>3</sub>).

## Aldehyde 3.32



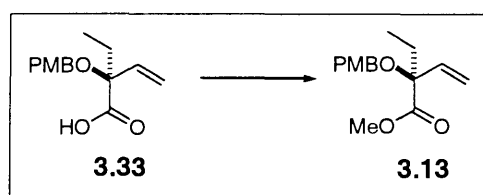
To a stirred solution of DMSO (20.6 mL, 291.0 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (300 mL) at  $-78^\circ\text{C}$  under  $\text{N}_2$  was added dropwise  $(\text{COCl})_2$  (12.7 mL, 145.5 mmol). Then a solution of alcohol **3.14** (11.45 g, 48.5 mmol) in  $\text{CH}_2\text{Cl}_2$  (100 mL) was added via cannula over 10 min. Then  $\text{Et}_3\text{N}$  (102.1 mL, 727.5 mmol) was added over 15 min, and the reaction mixture was stirred at  $-78^\circ\text{C}$  for 10 min before warming to rt over 40 min. The reaction mixture was quenched with brine, the organic layer was separated and the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (2 x 300 mL). The combined organics were dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo*. The residue was taken on to the next step without further purification. Data for **3.32**:  $[\alpha]_D -15.7^\circ$  ( $c$  0.95,  $\text{CH}_2\text{Cl}_2$ ); IR (neat)  $\text{cm}^{-1}$ : 3469 (w), 2971 (s), 2937 (s), 2837 (m), 1724 (s), 1612 (s), 1514 (s), 1462 (s), 1249 (s), 1173 (m), 1034 (m), 824 (m);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.52 (1H, s,  $\text{HCO}$ ), 7.30 (2H, d,  $J = 8.7$  Hz,  $\text{ArH}$ ), 6.88 (2H, d,  $J = 8.7$  Hz,  $\text{ArH}$ ), 5.76 (1H, dd,  $J = 17.7, 10.9$  Hz,  $\text{HHC=CH}$ ), 5.47 (1H, dd,  $J = 17.7, 1.1$  Hz,  $\text{HHC=CH}$ ), 5.46 (1H, dd,  $J = 10.9, 1.1$  Hz,  $\text{H}_2\text{C=CH}$ ), 4.42 (2H, m,  $\text{OCH}_2\text{Ar}$ ), 3.78 (3H, s,  $\text{ArOCH}_3$ ), 1.96 (1H, m,  $\text{CHHCH}_3$ ), 1.84 (1H, m,  $\text{CHHCH}_3$ ), 0.91 (3H, t,  $J = 7.5$  Hz,  $\text{CH}_2\text{CH}_3$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  201.7, 159.2, 134.3, 130.3, 129.0, 119.5, 113.8, 86.2, 65.7, 55.2, 25.7, 7.0; HRMS (FAB+) Calcd. for  $\text{C}_{14}\text{H}_{18}\text{O}_3\text{Na}$  ( $\text{M}+\text{Na}$ ) $^+$ : 257.11536. Found: 257.11466.

## Carboxylic acid 3.33



To a solution of crude aldehyde **3.32** (< 48.5 mmol) in *t*-BuOH (150 mL) and 2-methyl-2-butene (75 mL) at rt was added in 3 portions a solution of NaClO<sub>2</sub> (80 % purity, 16.45 g, 145.5 mmol) and NaH<sub>2</sub>PO<sub>4</sub> (17.44 g, 145.5 mmol) in H<sub>2</sub>O (150 mL). The reaction mixture was stirred at rt for 1 h, before dilution with saturated aqueous NH<sub>4</sub>Cl solution (200 mL) and extraction of the carboxylic acid product with EtOAc (3 x 200 mL). The combined organics were dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. The crude carboxylic acid **3.33** was used in the next step without any further purification. Data for **3.33**: [ $\alpha$ ]<sub>D</sub> -10.4 ° (*c* 0.46, CH<sub>2</sub>Cl<sub>2</sub>); IR (neat) cm<sup>-1</sup>: 2973 (br s), 1714 (s), 1613 (s), 1515 (s), 1463 (m), 1251 (m), 1175 (m), 1035 (m), 934 (m), 824 (m); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  10.50 (1H, br s, CO<sub>2</sub>H), 7.30 (2H, m, ArH), 6.88 (2H, m, ArH), 5.98 (1H, dd, *J* = 17.6, 10.9 Hz, HHC=CH), 5.50 (1H, dd, *J* = 17.6, 0.9 Hz, HHC=CH), 5.43 (1H, dd, *J* = 10.9, 0.9 Hz, H<sub>2</sub>C=CH), 4.43 (2H, m, OCH<sub>2</sub>Ar), 3.79 (3H, s, ArOCH<sub>3</sub>), 2.10 (1H, m, CHHCH<sub>3</sub>), 1.96 (1H, m, CHHCH<sub>3</sub>), 0.96 (3H, t, *J* = 7.4 Hz, CH<sub>2</sub>CH<sub>3</sub>); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  201.7, 159.2, 134.3, 130.3, 129.0, 119.5, 113.8, 86.2, 65.7, 55.2, 25.7, 7.0; HRMS (FAB+) Calcd. for C<sub>14</sub>H<sub>18</sub>O<sub>4</sub>Na (M+Na)<sup>+</sup>: 273.11027. Found: 273.10921.

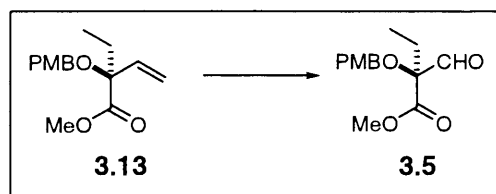
### Methyl ester **3.13**



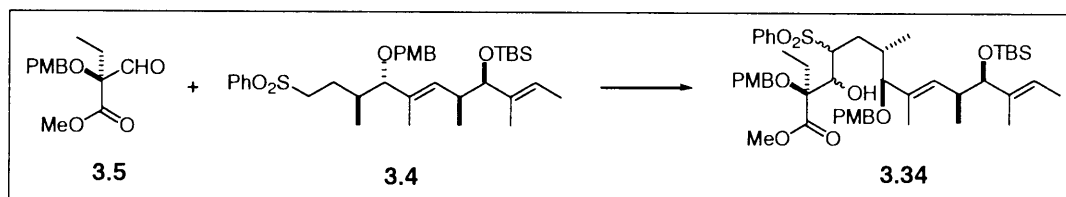
To a solution of crude carboxylic acid **3.33** (< 48.5 mmol) in anhydrous DMF (100 mL) was added K<sub>2</sub>CO<sub>3</sub> (20.08 g, 145.5 mmol) in one portion, followed by MeI (22.7 mL, 363.8 mmol) in one portion. The reaction mixture was stirred at rt for 1 h before addition of H<sub>2</sub>O (100 mL) and extraction of the carboxylic ester product with EtOAc (3 x 200 mL). The combined organics were washed with water (200 mL) and brine (200 mL), dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. Purification by SiO<sub>2</sub> flash chromatography (gradient elution 25:1 to 10:1 petrol/EtOAc) gave 10.75 g (84% over 3 steps) of ester **3.13** as a thick, colourless oil.

Data for **3.13**:  $[\alpha]_D$  -16.6 ° (*c* 1.0, CH<sub>2</sub>Cl<sub>2</sub>); IR (neat) cm<sup>-1</sup>: 2937 (s), 1734 (s), 1612 (s), 1514 (s), 1462 (s), 1381 (m), 1134 (s), 1093 (m), 1035 (m), 824 (s); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.31 (2H, m, ArH), 6.86 (2H, m, ArH), 6.01 (1H, dd, *J* = 17.6, 10.9 Hz, HHC=CH), 5.42 (1H, dd, *J* = 17.6, 1.2 Hz, HHC=CH), 5.34 (1H, dd, *J* = 10.9, 1.2 Hz, H<sub>2</sub>C=CH), 4.41 (2H, m, OCH<sub>2</sub>Ar), 3.76 (3H, s, ArOCH<sub>3</sub>), 3.75 (3H, s, CO<sub>2</sub>CH<sub>3</sub>), 1.99 (1H, m, CHHCH<sub>3</sub>), 1.91 (1H, m, CHHCH<sub>3</sub>), 0.90 (3H, t, *J* = 7.4 Hz, CH<sub>2</sub>CH<sub>3</sub>); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ; HRMS (FAB+) Calcd. for C<sub>15</sub>H<sub>20</sub>O<sub>4</sub>Na (M+Na)<sup>+</sup>: 287.12592. Found: 287.125213.

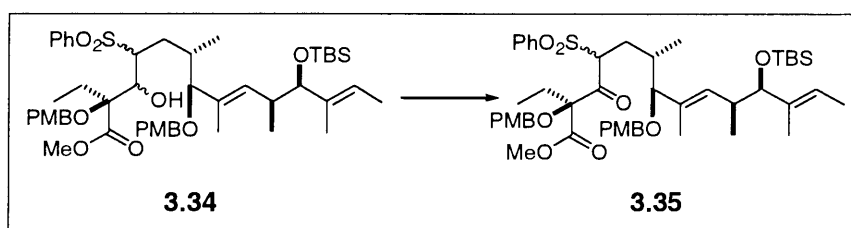
### Aldehyde 3.5



Carboxylic ester **3.13** (10.60 g, 40.1 mmol) was dissolved in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (250 mL) and anhydrous MeOH (12.5 mL). The solution was cooled to -78 °C, and O<sub>2</sub> was bubbled through it for 1 min. Then O<sub>3</sub> was bubbled through the solution for 1.5 h, at which point the reaction mixture had turned a pale blue colour. The reaction mixture was quenched by the addition of Me<sub>2</sub>S (29.4 mL, 401.0 mmol) and allowed to warm to rt. The mixture was stirred at rt for 30 min, and then concentrated *in vacuo*. The crude aldehyde was purified by SiO<sub>2</sub> flash chromatography (gradient elution 5:1 to 2:1 petrol/EtOAc) to give 7.90 g (74%) of aldehyde **3.5** as a colourless oil. Data for **3.5**:  $[\alpha]_D$  -13.0 ° (*c* 1.23, CH<sub>2</sub>Cl<sub>2</sub>); IR (neat) cm<sup>-1</sup>: 2955 (s), 1728 (s), 1612 (s), 1514 (s), 1459 (s), 1381 (m), 1251 (m), 1034 (m), 824 (m); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 9.72 (1H, s, HCO), 7.34 (2H, m, ArH), 6.87 (2H, m, ArH), 4.52 (2H, m, OCH<sub>2</sub>Ar), 3.80 (3H, s, ArOCH<sub>3</sub>), 3.79 (3H, s, CO<sub>2</sub>CH<sub>3</sub>), 2.06 (2H, m, CHHCH<sub>3</sub>), 0.93 (3H, t, *J* = 7.5 Hz, CH<sub>2</sub>CH<sub>3</sub>); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 198.4, 169.5, 159.4, 129.7, 129.5, 113.8, 88.1, 68.0, 55.3, 52.6, 26.5, 7.3.

**$\beta$ -Hydroxysulfone 3.34**

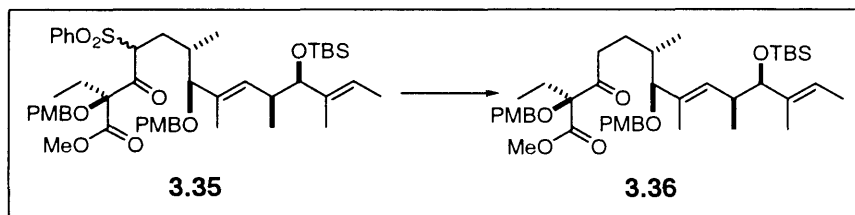
To a solution of phenylsulfone **3.4** (1.31 g, 2.13 mmol, azeotroped from benzene) in anhydrous THF (8 mL) at  $-78^{\circ}\text{C}$  under  $\text{N}_2$  was added dropwise  $n\text{-BuLi}$  (2.5 M, 0.94 mL, 2.34 mmol). The resultant yellow / orange solution was stirred at  $-78^{\circ}\text{C}$  for 30 min. This solution was then cannulated into a  $-78^{\circ}\text{C}$  solution of aldehyde **3.5** (0.74 g, 2.77 mmol) in anhydrous THF (8 mL) over 2 min. The reaction mixture was stirred at  $-78^{\circ}\text{C}$  for 20 min, then warmed to rt over 30 min. The reaction mixture was quenched by addition of brine, and the product was extracted with  $\text{Et}_2\text{O}$  (3 x 40 mL). The combined organics were dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo*. Purification by  $\text{SiO}_2$  flash chromatography (gradient elution 5:1 to 1:1 petrol:EtOAc) gave hydroxysulfone **3.34** as a mixture of diastereoisomers which was used directly in the next step.

 **$\beta$ -Ketosulfone 3.35**

To a solution of DMSO (0.91 mL, 12.8 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (20 mL) at  $-78^{\circ}\text{C}$  under  $\text{N}_2$  was added TFAA (0.90 mL, 6.39 mmol). The resulting mixture was stirred at  $-78^{\circ}\text{C}$  for 20 min, before a solution of sulfone **3.34** (< 2.13 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (20 mL) was added via cannula over 3 min. After 5 min at  $-78^{\circ}\text{C}$ ,  $\text{Et}_3\text{N}$  (5.9 mL, 42.6 mmol) was added dropwise, and the reaction mixture was allowed to warm to rt over 30 min. The reaction mixture was

then quenched with brine (20 mL). The organic layer was separated, and the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 20 mL). The combined organics were concentrated *in vacuo*, and the crude  $\beta$ -ketosulfone **3.35** was used in the next step without further purification.

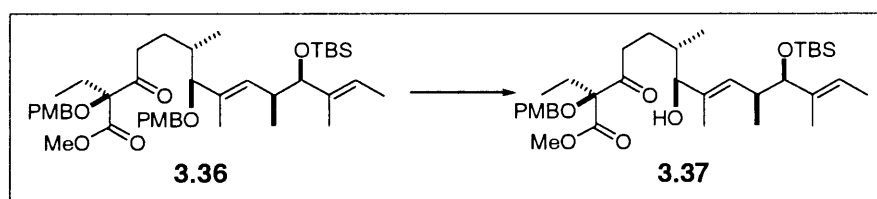
### Ketone 3.36



Crude ketosulfone **3.35** (< 2.13 mmol) was dissolved in THF- $\text{H}_2\text{O}$  (275 mL, 10:1 v:v) and the resultant solution was heated to reflux. Activated Al-Hg was added over 20 min, at which point the starting material had been consumed. The activated Al-Hg was prepared by dipping strips of aluminium foil sequentially into a 2% aqueous  $\text{HgCl}_2$  solution, MeOH and  $\text{Et}_2\text{O}$ . The reaction mixture was then cooled to rt and filtered through celite, the filter cake being washed thoroughly with EtOAc. The filtrate was dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo*. Purification by  $\text{SiO}_2$  flash chromatography (10:1 petrol/EtOAc) gave 1.20 g (76% over 3 steps) of ketone **3.36** as a thick, colourless oil. Data for **3.36**:  $[\alpha]_{\text{D}} +4.1^\circ$  (c 0.17,  $\text{CH}_2\text{Cl}_2$ ); IR (neat)  $\text{cm}^{-1}$ : 2956 (s), 2930 (s), 2856 (s), 1748 (s), 1720 (s), 1613 (m), 1586 (w), 1514 (s), 1461 (m), 1383 (w), 1301 (m), 1249 (s), 1176 (m), 1039 (s), 835 (s), 775 (m), 669 (w), 517 (w);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.28 (2H, d,  $J = 8.6$  Hz, ArH), 7.20 (2H, d,  $J = 8.5$  Hz, ArH), 6.85 (2H, d,  $J = 8.6$  Hz, ArH), 6.81 (2H, d,  $J = 8.6$  Hz, ArH), 5.31 (1H, q,  $J = 6.5$  Hz,  $\text{C}=\text{CHCH}_3$ ), 4.97 (1H, d,  $J = 9.7$  Hz,  $\text{C}=\text{CHCHCH}_3$ ), 4.38 (1H, d,  $J = 10.7$  Hz,  $\text{OCHHAr}$ ), 4.30 (1H, d,  $J = 10.7$  Hz,  $\text{OCHHAr}$ ), 4.20 (1H, d,  $J = 11.3$  Hz,  $\text{OCHHAr}$ ), 3.92 (1H, d,  $J = 11.3$  Hz,  $\text{OCHHAr}$ ), 3.78 (3H, s,  $\text{ArOCH}_3$ ), 3.76 (3H, s,  $\text{ArOCH}_3$ ), 3.67 (3H, s,  $\text{CO}_2\text{CH}_3$ ), 3.66 (1H, d,  $J = 8.9$  Hz,  $\text{CHOTBS}$ ), 3.09 (1H, d,  $J = 9.5$  Hz,  $\text{CHOPMB}$ ), 2.72-2.58 (3H, m,  $\text{CH}_2\text{C}=\text{O}$ ,  $\text{CHCH}_3$ ), 2.19 (1H, m,  $\text{CHHCH}_3$ ), 2.05 (1H, m,  $\text{CHHCH}_3$ ), 1.99 (1H, m,  $\text{CHHCH}_2\text{C}=\text{O}$ ), 1.61 (1H, m,  $\text{CHCH}_3$ ), 1.53 (3H, s,  $\text{CH}_3$ ), 1.50 (3H, s,  $\text{CH}_3$ ), 1.47 (3H, d,  $J = 6.6$  Hz,  $\text{CH}_3$ ), 1.24 (1H, m,  $\text{CHHCH}_2\text{C}=\text{O}$ ), 0.96 (3H, d,  $J = 6.6$  Hz,  $\text{CH}_3\text{CHCHOTBS}$ ), 0.87 (9H, s,  $(\text{CH}_3)_3\text{C}$ ), 0.81 (3H, t,  $J = 7.4$  Hz,

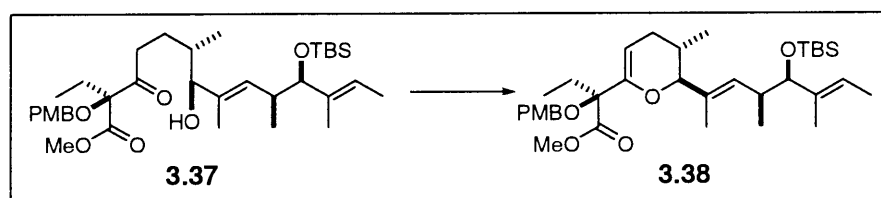
CH<sub>3</sub>CH<sub>2</sub>), 0.59 (3H, d,  $J$  = 6.8 Hz, CH<sub>3</sub>CHCHOPMB), 0.02 (3H, s, CH<sub>3</sub>Si), -0.05 (3H, s, CH<sub>3</sub>Si); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 208.2, 169.9, 159.2, 158.9, 138.1, 133.8, 131.8, 129.8, 129.5, 128.9, 121.2, 113.7, 113.6, 90.0, 89.8, 83.9, 69.0, 66.5, 55.25, 55.20, 52.4, 37.3, 36.5, 34.5, 29.7, 26.9, 25.9, 24.5, 18.2, 18.0, 16.0, 13.0, 10.7, 10.5, 7.3, -4.6, -5.1; HRMS (FAB+) Calcd. for C<sub>43</sub>H<sub>66</sub>O<sub>8</sub>SiNa (M+Na)<sup>+</sup>: 761.44244. Found: 761.44332.

### Hydroxyketone 3.37



To a solution of ketone **3.36** (2.20 g, 2.98 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (54 mL) and H<sub>2</sub>O (3 mL) was added DDQ (0.74 g, 3.27 mmol) at 0 °C. The resulting dark red solution was stirred at 0 °C for 3 h. Saturated NaHCO<sub>3</sub> solution (20 mL) was then added and the product was extracted with CH<sub>2</sub>Cl<sub>2</sub> (4 x 30 mL). The combined organics were washed with saturated NaHCO<sub>3</sub> solution (2 x 50 mL), dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. The crude product was used in the next step without further purification as a mixture of α- and β-hemiketals and hydroxyketone **3.37** (which was the major component of the equilibrium mixture).

### Glycal 3.38

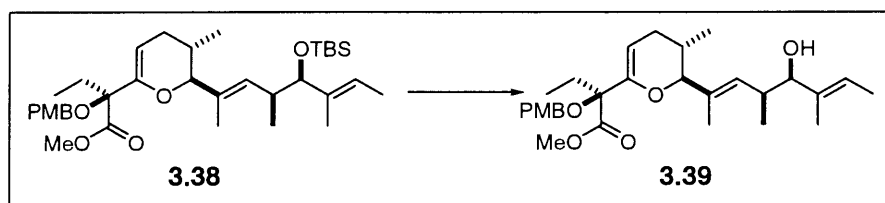


To a solution of crude hydroxyketone **3.37** (< 2.98 mmol) in anhydrous MeOH (40 mL) was added PPTS (0.19 g, 0.74 mmol) in one portion. The reaction mixture was refluxed at 60 °C for 1.5 h. The reaction mixture was then cooled to rt, and saturated NaHCO<sub>3</sub> solution (20 mL)



was added. The product was extracted with EtOAc (3 x 50 mL) and then dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. The residue was purified by SiO<sub>2</sub> flash chromatography (gradient elution 30:1 to 20:1 petrol:EtOAc) to give 1.79 g (81% over 2 steps) of glycal **3.38** as a clear oil. Data for **3.38**: [ $\alpha$ ]<sub>D</sub> +51.6 ° (*c* 0.31, CH<sub>2</sub>Cl<sub>2</sub>); IR (neat) cm<sup>-1</sup>: 2955 (s), 2930 (s), 2857 (s), 1743 (s), 1671 (m), 1614 (m), 1514 (s), 1459 (m), 1382 (m), 1302 (m), 1249 (s), 1131 (m), 1084 (s), 1043 (s), 857 (m), 836 (m), 775 (m); <sup>1</sup>H NMR (500 MHz, C<sub>6</sub>D<sub>6</sub>):  $\delta$  7.43 (2H, d, *J* = 8.5 Hz, ArH), 6.83 (2H, d, *J* = 8.6 Hz, ArH), 5.38 (1H, q, *J* = 6.5 Hz, C=CHCH<sub>3</sub>), 5.14-5.10 (2H, m, C=CHCHCH<sub>3</sub>, CH=C(C)O), 4.76 (1H, d, *J* = 10.7 Hz, OCHHAr), 4.51 (1H, d, *J* = 10.7 Hz, OCHHAr), 3.76 (1H, d, *J* = 7.5 Hz, CHOTBS), 3.66 (1H, d, *J* = 9.5 Hz, CHOC=C), 3.45 (3H, s, ArOCH<sub>3</sub>), 3.32 (3H, s, CO<sub>2</sub>CH<sub>3</sub>), 2.65 (1H, m, CHCH<sub>3</sub>CHOTBS), 2.30 (1H, m, CHHCH<sub>3</sub>), 2.21 (1H, m, CHHCH<sub>3</sub>), 1.93 (2H, m, CH<sub>2</sub>CH=C), 1.71 (1H, m, CH<sub>2</sub>CH(CH<sub>3</sub>)CO), 1.57-1.55 (9H, m, CH<sub>3</sub>C=C), 1.08 (3H, d, *J* = 6.6 Hz, CH<sub>3</sub>CHCHOTBS), 1.06 (3H, t, *J* = 7.4 Hz, CH<sub>3</sub>CH<sub>2</sub>), 1.02 (9H, s, (CH<sub>3</sub>)<sub>3</sub>C), 0.65 (3H, d, *J* = 6.6 Hz, CH<sub>2</sub>CHCH<sub>3</sub>), 0.12 (3H, s, CH<sub>3</sub>Si), 0.06 (3H, s, CH<sub>3</sub>Si); <sup>13</sup>C NMR (125 MHz, C<sub>6</sub>D<sub>6</sub>):  $\delta$  172.0, 159.6, 153.4, 137.5, 133.2, 132.3, 131.7, 129.4, 128.5, 128.3, 128.2, 128.0, 127.9, 127.8, 121.1, 113.9, 98.3, 88.0, 84.4, 83.0, 66.9, 54.7, 51.4, 37.4, 29.4, 29.0, 26.7, 26.1, 18.5, 17.5, 17.3, 13.0, 11.7, 11.3, 8.2, -4.4, -4.9; HRMS (FAB+) Calcd. for C<sub>43</sub>H<sub>66</sub>O<sub>8</sub>SiNa (M+Na)<sup>+</sup>: 623.37437. Found: 623.37306.

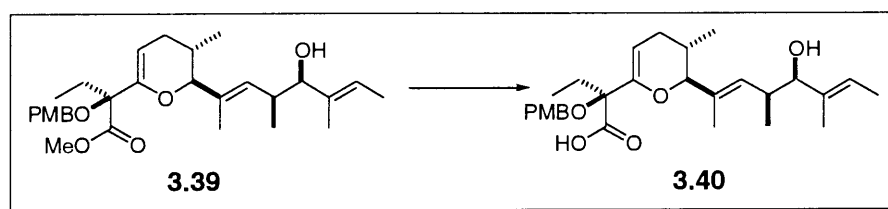
### Alcohol 3.39



To 20 mL of 1.0 M TBAF in THF was added 20 mL of anhydrous DMF. The THF was then removed under reduced pressure on a rotary evaporator to give a 1.0 M solution of TBAF in DMF. This 1.0 M solution of TBAF in DMF was transferred to a flask containing neat glycal **3.38** (1.19 g, 1.98 mmol). The resultant mixture was stirred at rt under N<sub>2</sub> for 12 h. The reaction mixture was then diluted with Et<sub>2</sub>O (50 mL) and washed with H<sub>2</sub>O (2 x 25 mL). The

organic layer was dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo*. The residue was purified by  $\text{SiO}_2$  flash chromatography (gradient elution 10:1 to 5:1 petrol/EtOAc) to give 735 mg (76%) of alcohol **3.39** as a clear oil. Data for **3.39**: IR (neat)  $\text{cm}^{-1}$ : 3457 (br m), 2954 (s), 2925 (s), 2871 (s), 1742 (s), 1670 (m), 1613 (m), 1514 (s), 1456 (s), 1380 (m), 1302 (m), 1248 (s), 1131 (m), 1082 (m), 1037 (m), 1013 (m), 823 (m);  $^1\text{H}$  NMR (500 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta$  7.43 (2H, d,  $J$  = 8.8 Hz, ArH), 6.84 (2H, d,  $J$  = 8.7 Hz, ArH), 5.39 (1H, qt,  $J$  = 6.5, 1.0 Hz,  $\text{C}=\text{CHCH}_3$ ), 5.20 (1H, dd,  $J$  = 9.7, 1.0 Hz,  $\text{C}=\text{CHCHCH}_3$ ), 5.07 (1H, dd,  $J$  = 5.4, 2.3 Hz,  $\text{CH}_2\text{CH}=\text{C}(\text{C})\text{O}$ ), 4.79 (1H, d,  $J$  = 10.8 Hz,  $\text{OCHHAr}$ ), 4.52 (1H, d,  $J$  = 10.8 Hz,  $\text{OCHHAr}$ ), 3.67 (1H, d,  $J$  = 6.7 Hz,  $\text{CHOH}$ ), 3.60 (1H, d,  $J$  = 9.5 Hz,  $\text{CHOC}=\text{C}$ ), 3.45 (3H, s,  $\text{ArOCH}_3$ ), 3.29 (3H, s,  $\text{CO}_2\text{CH}_3$ ), 2.61 (1H, m,  $\text{CHCH}_3\text{CHOH}$ ), 2.28 (1H, m,  $\text{CHHCH}_3$ ), 2.19 (1H, m,  $\text{CHHCH}_3$ ), 1.92 (1H, dt,  $J$  = 16.7, 5.2 Hz,  $\text{CH}_2\text{CH}=\text{C}$ ), 1.68 (1H, m,  $\text{CH}_2\text{CH}(\text{CH}_3)\text{CO}$ ), 1.56-1.51 (9H, m,  $\text{CH}_3\text{C}=\text{C}$ ), 1.08 (3H, d,  $J$  = 6.7 Hz,  $\text{CH}_3\text{CHCHOH}$ ), 1.04 (3H, t,  $J$  = 7.4 Hz,  $\text{CH}_3\text{CH}_2$ ), 0.62 (3H, d,  $J$  = 6.6 Hz,  $\text{CH}_2\text{CHCH}_3$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta$  172.2, 159.5, 151.3, 137.9, 133.3, 132.3, 131.8, 129.5, 128.5, 128.3, 128.2, 128.0, 127.9, 127.8, 120.7, 113.9, 98.6, 87.8, 84.6, 81.4, 66.9, 54.8, 51.4, 36.4, 29.4, 28.9, 27.0, 17.5, 16.6, 13.0, 11.9, 11.2, 8.2; HRMS (FAB+) Calcd. for  $\text{C}_{29}\text{H}_{42}\text{O}_6\text{Na}$  ( $\text{M} + \text{Na}$ ) $^+$ : 509.28789. Found: 509.286393.

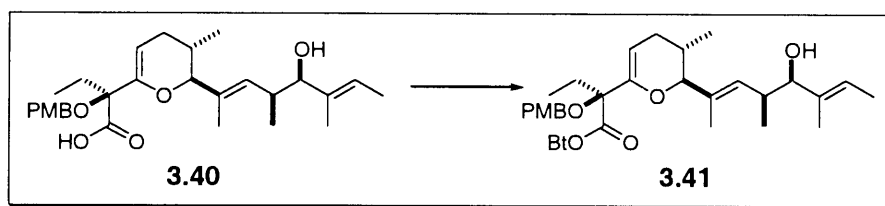
### Carboxylic acid **3.40**



To a solution of EtSH (0.53 mL, 7.55 mmol) in dry THF (8 mL) at 0 °C under  $\text{N}_2$  was added *n*-BuLi (2.5 M in hexanes, 2.78 mL, 6.95 mmol). The resultant cloudy solution was stirred at 0 °C for 30 min. Then a solution of alcohol **3.39** (735 mg, 1.51 mmol) in anhydrous HMPA (16 mL) was added over 2 min. The reaction mixture was warmed to rt, and stirred at rt for 2 h. The reaction mixture was diluted with EtOAc (50 mL) and acidified to pH 6 with 2 M aqueous  $\text{NaHSO}_4$ . The organic layer was separated, and the aqueous phase extracted with EtOAc.

The aqueous layer was then further acidified to pH 4 with 2 M aqueous  $\text{NaHSO}_4$  and re-extracted with EtOAc. The combined organics were washed with water (50 mL) and brine (50 mL), dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo*. The crude product, acid **3.40**, was used in the next step without further purification.

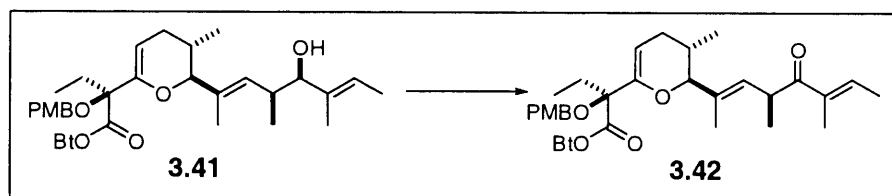
#### *N*-Hydroxybenzotriazolyl ester **3.41**



To a solution of crude acid **3.40** (<1.51 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (15 mL) at rt under  $\text{N}_2$  was added *i*-PrNEt<sub>2</sub> (0.9 mL) followed by BOP reagent (1.34 g, 3.02 mmol). The reaction mixture was stirred at rt for 10 min, then diluted with EtOAc (50 mL) and washed with  $\text{H}_2\text{O}$  (2 x 25 mL). The organic layer was then dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo*. The residue was purified by  $\text{SiO}_2$  flash chromatography (gradient elution 10:1 to 5:1 petrol/EtOAc) to give 710 mg (80% for 2 steps) of activated ester **3.41** as a clear oil. Data for **3.41**:  $[\alpha]_D^{+65.4}$  (c 0.67,  $\text{CH}_2\text{Cl}_2$ ); IR (neat)  $\text{cm}^{-1}$ : 3424 (br s), 2925 (s), 2872 (s), 2838 (m), 1816 (s), 1671 (m), 1613 (m), 1514 (s), 1456 (m), 1380 (m), 1302 (m), 1248 (s), 1037 (s), 822 (m), 743 (m);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.04 (1H, d,  $J$  = 8.4 Hz, ArH), 7.51-7.48 (1H, m, ArH), 7.40-7.33 (4H, m, ArH), 6.86 (2H, d,  $J$  = 8.7 Hz, ArH), 5.43 (1H, q,  $J$  = 6.6 Hz,  $\text{C}=\text{CHCH}_3$ ), 5.37 (1H, d,  $J$  = 10.7 Hz,  $\text{C}=\text{CHCHCH}_3$ ), 5.26 (1H, dd,  $J$  = 5.4, 2.2 Hz,  $\text{CH}_2\text{CH}=\text{C}(\text{C})\text{O}$ ), 4.68 (1H, d,  $J$  = 10.5 Hz,  $\text{OCH}_2\text{HAr}$ ), 4.53 (1H, d,  $J$  = 10.5 Hz,  $\text{OCH}_2\text{HAr}$ ), 3.85 (1H, d,  $J$  = 6.7 Hz,  $\text{CH}_2\text{OH}$ ), 3.83 (1H, d,  $J$  = 9.6 Hz,  $\text{CH}_2\text{OC}=\text{C}$ ), 3.78 (3H, s,  $\text{ArOCH}_3$ ), 2.65 (1H, m,  $\text{CH}_2\text{CH}_3\text{CHOH}$ ), 2.28-2.21 (3H, m,  $\text{CH}_3\text{CH}_2$ ,  $\text{CH}_2\text{HCH}=\text{C}$ ), 1.95-1.83 (2H, m,  $\text{CH}_2\text{CH}(\text{CH}_3)\text{CO}$ ,  $\text{CH}_2\text{CH}=\text{C}$ ), 1.66 (3H, d,  $J$  = 1.3 Hz,  $\text{CH}_3\text{C}=\text{CHCHCH}_3$ ), 1.55 (3H, s,  $\text{CH}_3\text{C}=\text{CHCH}_3$ ), 1.51 (3H, d,  $J$  = 6.7 Hz,  $\text{CH}_3\text{CH}=\text{C}$ ), 1.08 (3H, t,  $J$  = 7.4 Hz,  $\text{CH}_3\text{CH}_2$ ), 0.98 (3H, d,  $J$  = 6.7 Hz,  $\text{CH}_3\text{CH}(\text{C})\text{CHOH}$ ), 0.83 (3H, d,  $J$  = 6.5 Hz,  $\text{CH}_2\text{CHCH}_3$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  168.3, 159.2, 149.1, 143.4, 136.9, 133.5, 131.9, 130.0, 129.3, 128.7, 128.6, 124.7, 121.0, 120.5,

113.7, 108.4, 106.4, 88.3, 84.1, 80.9, 66.9, 55.3, 35.9, 29.4, 29.1, 26.4, 17.4, 15.8, 12.9, 12.1, 11.6, 7.7; HRMS (FAB+) Calcd. for  $C_{34}H_{43}N_3O_6$  ( $M+Na$ )<sup>+</sup>: 612.30494. Found: 612.30501.

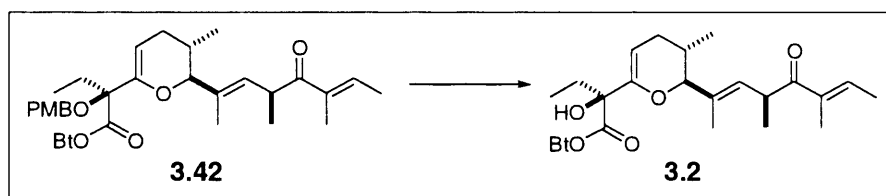
### Ketone 3.42



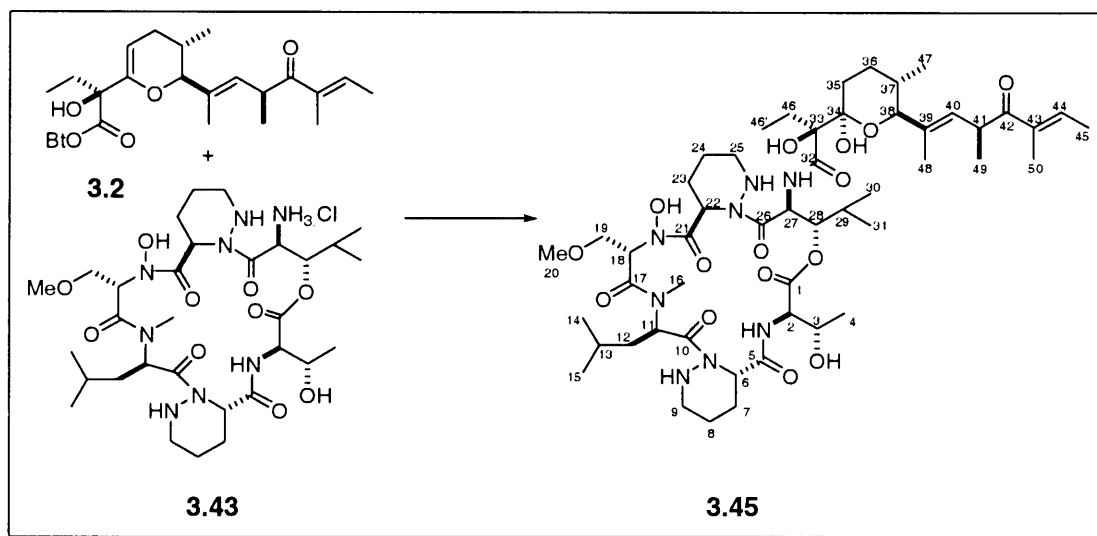
To a stirred solution of DMSO (0.16 mL, 2.24 mmol) in anhydrous  $CH_2Cl_2$  (5 mL) at  $-78\text{ }^{\circ}C$  under  $N_2$  atmosphere was added TFAA (0.16 mL, 1.12 mmol) dropwise. The mixture was stirred at  $-78\text{ }^{\circ}C$  for 20 min, and then a solution of alcohol **3.41** (220 mg, 0.37 mmol) in anhydrous  $CH_2Cl_2$  (5 mL) was added dropwise. The reaction mixture was stirred at  $-78\text{ }^{\circ}C$  for 5 min, then  $Et_3N$  (1.03 mL, 7.4 mmol) was added dropwise and the mixture was allowed to warm to rt over 30 min. The reaction mixture was then diluted with  $CH_2Cl_2$  (50 mL) and washed with brine (25 mL). The organic layer was separated, dried over  $MgSO_4$ , filtered and concentrated *in vacuo*. Purification by  $SiO_2$  flash chromatography (gradient elution 10:1 to 5:1 Petrol:EtOAc) gave 190 mg (87%) of ketone **3.42** as a thick, rose-tinted oil. Data for **3.42**: IR (neat)  $cm^{-1}$ : 3444 (br s), 2929 (s), 2872 (s), 2875 (m), 2838 (m), 1817 (m), 1664 (s), 1615 (m), 1514 (m), 1453 (m), 1381 (m), 1302 (m), 1248 (s), 1038 (s), 822 (m), 743 (m), 649 (w);  $^1H$  NMR (500 MHz,  $CDCl_3$ ):  $\delta$  8.03-8.00 (1H, m, ArH), 7.44-7.27 (5H, m, ArH), 6.85 (2H, m, ArH), 6.78 (1H, q,  $J = 6.2$  Hz,  $C=CHCH_3$ ), 5.68 (1H, d,  $J = 9.4$  Hz,  $C=CHCHCH_3$ ), 5.27 (1H, dd,  $J = 5.7, 2.0$  Hz,  $CH_2CH=C(C)O$ ), 4.67 (1H, d,  $J = 10.5$  Hz,  $OCHHAr$ ), 4.50 (1H, d,  $J = 10.6$  Hz,  $OCHHAr$ ), 4.16 (1H, m,  $CH_3CHC=O$ ), 3.92 (1H, d,  $J = 9.6$  Hz,  $CHOC=C$ ), 3.77 (3H, s,  $ArOCH_3$ ), 2.27-2.22 (3H, m,  $CH_3CH_2$ ,  $CHHCH=C$ ), 1.97-1.87 (2H, m,  $CH_2CH(CH_3)CO$ ,  $CHHCH=C$ ), 1.80-1.77 (6H, m,  $CH_3CH=C$ ,  $CH_3C=CHCH_3$ ), 1.72 (3H, d,  $J = 1.3$  Hz,  $CH_3C=CHCHCH_3$ ), 1.15 (3H, d,  $J = 6.9$  Hz,  $CH_3CH(C)CHOH$ ), 1.09 (3H, t,  $J = 7.4$  Hz,  $CH_3CH_2$ ), 0.84 (3H, d,  $J = 6.4$  Hz,  $CH_2CHCH_3$ );  $^{13}C$  NMR (125 MHz,  $CDCl_3$ ):  $\delta$  203.0, 168.2, 159.2, 149.1, 143.4, 137.7, 137.4, 133.0, 131.5, 130.0, 129.3, 128.8, 128.6, 124.7, 120.3,

113.7, 108.4, 100.6, 88.1, 84.0, 66.7, 55.3, 38.9, 29.3, 29.0, 26.4, 18.5, 17.3, 14.8, 11.4, 11.2, 7.8; HRMS (FAB+) Calcd. for  $C_{34}H_{41}N_3O_6$  ( $M+Na$ )<sup>+</sup>: 610.28929. Found: 610.29021.

### Alcohol **3.2**



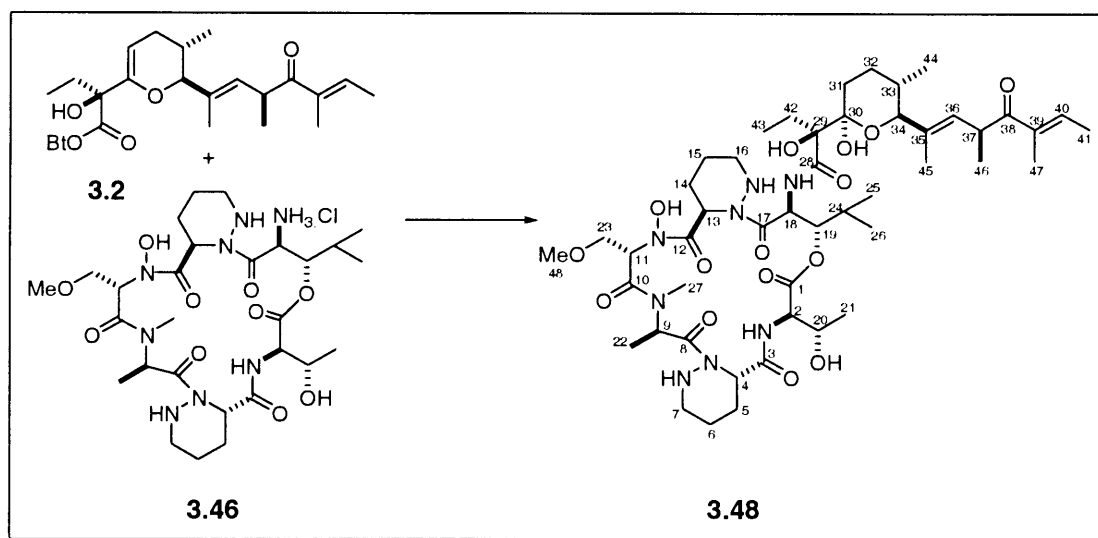
To a stirred solution of ketone **3.42** (190 mg, 0.32 mmol) in 20 mL of wet  $CDCl_3$  was added DDQ (190 mg, 0.83 mmol) at rt. The reaction mixture was stirred vigorously at rt for 3 h before being diluted with  $Et_2O$  (50 mL) and rapidly washed with saturated  $NaHCO_3$  solution (3 x 25 mL). A further wash with brine (25 mL) was carried out before the organic layer was dried over anhydrous  $MgSO_4$ , filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient elution 10:1 to 6:1 petrol:EtOAc) to give a colourless oil. A second chromatographic purification ( $SiO_2$ , 6:1 petrol:EtOAc) was then performed to rigorously ensure complete removal of any residual DDQ. This gave 116 mg (78%) of **3.2** as a colourless oil.

A83586C-Citropeptin hybrid **3.45**

To activated ester **3.2** (126 mg, 0.270 mmol) in a round-bottomed flask under  $N_2$  was added cyclodepsipeptide salt **3.43** (198 mg, 0.270 mmol). The flask was then cooled to  $-78\text{ }^{\circ}\text{C}$ , and DMF (1 mL) was added, followed by  $\text{Et}_3\text{N}$  (0.38 mL, 2.70 mmol) dropwise over 1 min. After addition, the dry ice bath was removed and the reaction mixture was stirred at  $0\text{ }^{\circ}\text{C}$  for 30 min. The reaction mixture was then diluted with  $\text{Et}_2\text{O}$  and washed sequentially with 0.5 M aq. HCl (15 mL), sat. aq.  $\text{NaHCO}_3$  solution (15 mL) and brine (15 mL). The organic layer was then dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The product was purified by preparative TLC using 40:1  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  as the eluent (eluted three times) to give 125 mg (40%) of **3.45** as a white solid. Data for **3.45**:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.95 (1H, s, N-OH), 7.99 (1H, d,  $J = 10.5$  Hz, 27-NHCO), 6.75 (1H, qd,  $J = 6.9, 1.3$  Hz, 44-CH), 6.20 (1H, d,  $J = 8.5$  Hz, 2-NHCO), 6.15 (1H, t,  $J = 7.5$  Hz, 11-CH), 5.55 (1H, dq,  $J = 9.2, 1.4$  Hz, 40-CH=), 5.47 (1H, dd,  $J = 10.7, 2.4$  Hz, 28-CH), 5.32 (1H, dd,  $J = 7.8, 6.5$  Hz, 18-CH), 5.19 (1H, dd,  $J = 6.0, 2.2$  Hz, 6-CH), 4.96 (1H, dd,  $J = 5.4, 2.3$  Hz, 35-CH=), 4.90 (1H, dd,  $J = 7.0, 2.8$  Hz, 22-CH), 4.89 (1H, t,  $J = 10.5$  Hz, 27-CH), 4.77 (1H, qdd,  $J = 6.5, 1.8, 1.0$  Hz, 3-CH), 4.51 (1H, dd,  $J = 8.5, 1.0$  Hz, 2-CH), 4.40 (1H, br s, 3-OH), 4.34 (1H, dd,  $J = 12.9, 2.3$  Hz, 25-NH), 4.10 (1H, dq,  $J = 9.2, 6.9$  Hz, 41-CH), 3.97 (1H, dd,  $J = 12.0, 2.3$  Hz, 9-NH), 3.86 (1H, dd,  $J = 10.1, 7.8$  Hz, 19-CH $\underline{\text{H}}$ ), 3.74 (1H, d,  $J = 9.5$  Hz, 38-CH), 3.72 (1H, dd,  $J = 10.1, 6.5$  Hz, 19-CH $\underline{\text{H}}$ ), 3.34 (3H, s, 20-OMe), 3.32 (1H, br m, 9-CH $\underline{\text{H}}$ ), 3.07 (1H, br m, 25-CH $\underline{\text{H}}$ ),

3.02 (3H, s, 16-Me), 2.96 (1H, br m, 25-CH<sub>2</sub>), 2.56 (1H, m, 7-CH<sub>2</sub>), 2.20 (1H, br m, 23-CH<sub>2</sub>), 2.07 (1H, m, 36-CH<sub>2</sub>), 1.90 (1H, m, 46-CH<sub>2</sub>), 1.87 (1H, br m, 23-CH<sub>2</sub>), 1.86 (3H, s, 45-Me), 1.80 (1H, m, 29-CH), 1.79 (1H, m, 46-CH<sub>2</sub>), 1.78 (1H, m, 37-CH), 1.77 (3H, s, 50-Me), 1.72 (2H, overlapping m, 36-CH<sub>2</sub>, 12-CH<sub>2</sub>), 1.69 (1H, m, 7-CH<sub>2</sub>), 1.64 (3H, d,  $J = 1.3$  Hz, 48-Me), 1.61 (1H, overlapping m, 8-CH<sub>2</sub>), 1.57 (1H, overlapping m, 24-CH<sub>2</sub>), 1.54 (1H, overlapping m, 8-CH<sub>2</sub>), 1.46 (1H, overlapping m, 12-CH<sub>2</sub>), 1.44 (2H, overlapping m, 13-CH, 24-CH<sub>2</sub>), 1.12 (3H, d,  $J = 6.9$  Hz, 49-Me), 1.04 (3H, dd,  $J = 6.5, 0.9$  Hz, 4-Me), 0.94 (3H, d,  $J = 6.5$  Hz, 14-Me), 0.94 (3H, d,  $J = 6.8$  Hz, 30-Me), 0.93 (3H, d,  $J = 6.5$  Hz, 15-Me), 0.83 (3H, d,  $J = 6.9$  Hz, 31-Me), 0.83 (3H, t, 46'-Me), 0.77 (3H, d,  $J = 6.5$  Hz, 47-Me); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  202.93 (42-CO), 173.77 (21-CONOH), 172.37 (10-CON), 171.41 (17-CON), 171.41 (26-CON), 171.33 (32-COO), 170.21 (1-COO), 169.58 (5-CONH), 151.19 (34-C), 137.57 (43-C=), 137.08 (44-CH=), 132.83 (39-C=), 130.96 (40-CH=), 96.67 (35-CH=), 87.72 (38-CH), 78.55 (33-C), 78.53 (28-CH), 68.56 (19-CH<sub>2</sub>), 64.81 (3-CH), 59.16 (20-OMe), 56.34 (2-CH), 55.27 (27-CH), 54.33 (18-CH), 52.39 (6-CH), 51.47 (22-CH), 50.26 (11-CH), 47.94 (9-CH<sub>2</sub>), 45.68 (25-CH<sub>2</sub>), 38.71 (41-CH), 36.62 (12-CH<sub>2</sub>), 30.67 (46-CH<sub>2</sub>), 29.87 (16-NMe), 29.83 (29-CH), 28.90 (37-CH), 28.86 (36-CH<sub>2</sub>), 24.73 (13-CH), 24.50 (7-CH<sub>2</sub>), 24.03 (23-CH<sub>2</sub>), 22.83 (14-Me), 22.78 (15-Me), 21.44 (8-CH<sub>2</sub>), 21.21 (24-CH<sub>2</sub>), 19.46 (31-Me), 18.98 (4-Me), 18.68 (49-Me), 17.31 (47-Me), 15.04 (30-Me), 14.87 (45-Me), 11.40 (50-Me), 11.26 (48-Me), 7.93 (46'-Me). Numbered as for citropeptin in Nakagawa et. al., reference 5 in the main text.

## Kettapeptin 3.48

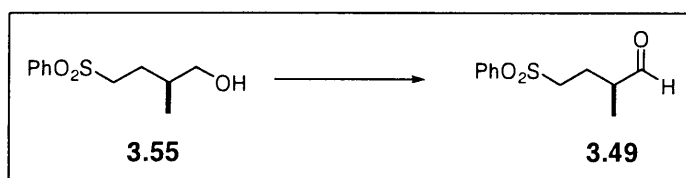


To activated ester **3.2** (110 mg, 0.236 mmol) in a round-bottomed flask under  $N_2$  was added the azinotricin cyclodipeptide salt **3.46** (163 mg, 0.236 mmol). The reaction flask was then cooled to  $-78^\circ C$ , and DMF (1 mL) and  $Et_3N$  (0.066 mL, 0.472 mmol) were added. The reaction mixture was stirred at  $-78^\circ C$  for 5 min, then gradually warmed to rt over 30 min. The reaction mixture was then diluted with  $Et_2O$  (25 mL) and washed sequentially with 0.5 M aq. HCl (10 mL), sat. aq.  $NaHCO_3$  solution (10 mL) and brine (10 mL). The organic layer was then dried over  $MgSO_4$  and concentrated under reduced pressure. The crude material was then purified by flash chromatography on silica gel (petrol/ $EtOAc$  5:1 to 1:1 as eluent) followed by preparative TLC using 15:1  $CH_2Cl_2/MeOH$  as the eluent, followed by another chromatographic purification on  $SiO_2$  with 20:1  $CH_2Cl_2/MeOH$ , to give 12 mg (5%) of kettapeptin as a white amorphous solid. Data for **3.48**:  $[\alpha]_D^{+56.4}$  ( $c$  0.22,  $CH_2Cl_2$ );  $^1H$  NMR (500 MHz,  $CDCl_3$ ):  $\delta$  9.92 (br s, 1H, NOH), 8.21 (1H, d,  $J = 10.7$  Hz, 18-NHCO), 6.72 (1H, q,  $J = 6.9$  Hz, 40-CH), 6.22 (1H, m, 2-CN $H$ ), 6.10 (1H, q,  $J = 7.0$  Hz, 9-CH), 5.61 (1H, d,  $J = 8.9$  Hz, 36-CH), 5.40 (1H, dd,  $J = 10.8, 2.0$  Hz, 19-CH), 5.32 (1H, t,  $J = 7.0$  Hz, 11-CH), 5.18 (1H, m, 4-CH), 4.91 (2H, m, 13-CH, 18-CH), 4.78 (1H, m, 20-CH), 4.52 (1H, m, 2-CH), 4.42-4.38 (2H, m, 16-CN $H$ , 20-COH), 4.06 (1H, m, 37-CH), 3.95 (1H, d,  $J = 10.2$  Hz, 34-CH), 3.84 (2H, m, 7-CN $H$ , 23-CH $H$ ), 3.74 (1H, m, 23-CH $H$ ), 3.35 (3H, s, 48-Me), 3.29 (1H, br m, 7-CH $H$ ), 3.14 (1H, br m, 16-CH $H$ ), 3.03 (3H, s, 27-Me), 2.97 (1H, m, 16-CH $H$ ), 2.55 (1H, br m, 5-CH $H$ ),



2.23 (1H, d,  $J = 13.4$  Hz, 14-CH $\underline{H}$ H), 2.01 (1H, m, 42-CH $\underline{H}$ H), 1.90-1.46 (11H, overlapped m, 5-CH $\underline{H}$ H, 6-CH $\underline{2}$ , 14-CH $\underline{H}$ H, 15-CH $\underline{2}$ , 24-CH, 31-CH, 32-CH, 33-CH, 42-CH), 1.84 (3H, d,  $J = 6.8$  Hz, 41-Me), 1.75 (3H, s, 47-Me), 1.56 (3H, s, 45-Me), 1.24 (3H, m, 22-Me), 1.10 (3H, d,  $J = 6.8$  Hz, 46-Me), 1.04 (3H, m, 21-Me), 0.84-0.80 (6H, m, 43-Me, 26-Me), 0.70-0.68 (25-Me, 44-Me);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  202.9 (C-38), 175.3 (C-28), 173.1 (C-8), 172.8 (C-12), 171.1 (C-10), 170.9 (C-17), 170.3 (C-1), 169.6 (C-3), 137.5 (C-39), 136.7 (C-40), 132.8 (C-35), 129.4 (C-36), 99.6 (C-30), 82.2 (C-34), 80.1 (C-29), 78.7 (C-19), 68.5 (C-23), 64.8 (C-20), 59.2 (C-48), 56.2 (C-2), 54.7 (C-18), 53.9 (C-11), 52.5 (C-4), 51.3 (C-13), 48.0 (C-7), 47.7 (C-9), 45.7 (C-16), 38.2 (C-37), 32.6 (C-33), 29.5 (C-27), 29.3 (C-24), 28.3 (C-31), 27.3 (C-32), 25.9 (C-42), 24.4 (C-5), 24.0 (C-14), 21.3 (C-6), 21.1 (C-15), 19.5 (C-46), 19.4 (C-25), 18.9 (C-21), 17.6 (C-44), 14.8 (C-41), 14.7 (C-26), 13.2 (C-22), 12.1 (C-45), 11.4 (C-47), 8.3 (C-43); HRMS (FAB+) Calcd. for  $\text{C}_{48}\text{H}_{78}\text{N}_8\text{O}_{15}$  ( $\text{M}+\text{Na}$ ) $^+$ : 1029.54841. Found: 1029.55053. Kettapeptin numbered as in Maskey et. al., reference 8 in the main text.

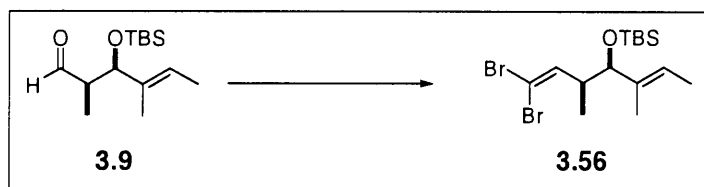
### Aldehyde 3.49



To a solution of anhydrous DMSO (7.45 mL, 105.0 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (100 mL) at  $-78^\circ\text{C}$  under  $\text{N}_2$  was added oxalyl chloride (4.59 mL, 52.6 mmol) dropwise over 5 min. The reaction mixture was stirred at  $-78^\circ\text{C}$  for 5 min, and a solution of alcohol **3.55**<sup>76</sup> (4.00 g, 17.5 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (20 mL + 5 mL wash) was added dropwise via syringe over 10 min. The reaction mixture was stirred at  $-78^\circ\text{C}$  for a further 10 min before addition of  $\text{Et}_3\text{N}$  (36.8 mL, 262.5 mmol) over 5 min. The reaction mixture was then stirred at  $-78^\circ\text{C}$  for another 10 min, and then allowed to warm to rt over 30 min. The reaction mixture was then quenched with brine (50 mL) and extracted with EtOAc (3 x 100 mL). The combined organics were washed with brine, dried over anhydrous  $\text{MgSO}_4$  and purified by flash chromatography on silica gel (petrol/EtOAc 5:1 to 2:1 as eluent) to give 3.80 g (96%) of aldehyde **3.49** as an oil. IR (neat)

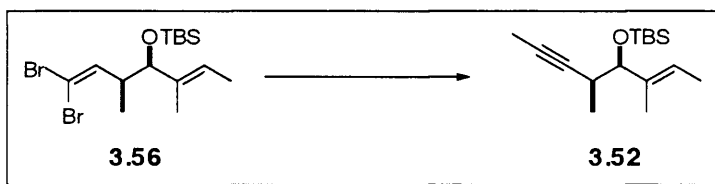
cm<sup>-1</sup>: 2971 (w), 1723 (s), 1448 (m), 1306 (s), 1147 (s), 1087 (m), 745 (m), 691 (m), 590 (w), 559 (w), 535 (m); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 9.53 (1H, d, *J* = 0.9 Hz, CH<sub>2</sub>O), 7.87-7.85 (2H, m, ArH), 7.64-7.61 (1H, m, ArH), 7.55-7.52 (2H, m, ArH), 3.15-3.03 (2H, m, PhSO<sub>2</sub>CH<sub>2</sub>), 2.51 (1H, m, CH(CH<sub>3</sub>)CHO), 2.03 (1H, m, PhSO<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 1.76 (1H, m, PhSO<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 1.09 (3H, d, *J* = 7.3 Hz, CH<sub>3</sub>); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 138.7, 133.8, 129.3, 127.9, 53.4, 44.5, 23.0, 13.3; HRMS (CI) Calcd. for C<sub>11</sub>H<sub>14</sub>O<sub>3</sub>S (M)<sup>+</sup>: 227.07419. Found: 227.07429.

### Dibromide 3.56



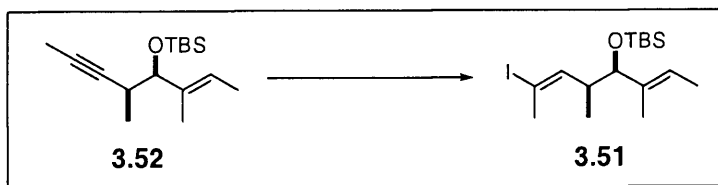
To a well stirred solution of Ph<sub>3</sub>P (2.66 g, 10.14 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (25 ml) at 0 °C under N<sub>2</sub> was added CBr<sub>4</sub> (1.68 g, 5.07 mmol) in one portion. The red/brown solution was stirred at 0 °C for 20 min whereafter a solution of the aldehyde **3.9** (1.0 g, 3.90 mmol) and Et<sub>3</sub>N (0.54 ml, 3.87 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (5 ml) was added dropwise over 2-3 min. The reactants were stirred at 0 °C for 10 min; TLC analysis of the reaction mixture at this stage indicated that all of the starting aldehyde **3.9** had been consumed, and that a single faster-moving product **3.56** had formed. Petrol (20 ml) was now added and the mixture was filtered through a short plug of SiO<sub>2</sub>, which was washed with neat petrol (100 ml). After removal of the solvents *in vacuo*, the crude residue was purified by SiO<sub>2</sub> flash chromatography using neat petrol as the eluent; the dibromoalkene **3.56** (1.49 g, 93%) was isolated as a colourless oil that was used directly for the next step. NMR data for **3.56**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 6.11 (d, 1H, *J* = 9.6 Hz, Br<sub>2</sub>C=CH), 5.34 (q, 1H, *J* = 1.0, 6.7 Hz, CH<sub>3</sub>CH=C(CH<sub>3</sub>)-), 3.78 (d, 1H, *J* = 6.7 Hz, CH(OTBS)), 2.55 (m, 1H, CH(CH<sub>3</sub>)CH(OTBS)), 1.57 (d, 3H, *J* = 6.8 Hz, CH<sub>3</sub>CH=C(CH<sub>3</sub>)-), 1.53 (s, 3H, CH<sub>3</sub>CH=C(CH<sub>3</sub>)), 0.97 (d, 3H, *J* = 6.7 Hz, CH(CH<sub>3</sub>)CH(OTBS)), 0.87 (s, 9H, *t*-Bu(CH<sub>3</sub>)<sub>2</sub>SiO), 0.00 (s, 3H, *t*-Bu(CH<sub>3</sub>)<sub>2</sub>SiO), -0.07 (s, 3H, *t*-Bu(CH<sub>3</sub>)<sub>2</sub>SiO); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 142.1, 136.4, 121.1, 87.3, 80.6, 42.9, 25.8, 18.2, 14.6, 12.9, 11.8, -4.7, -5.2.

## Methyl acetylene 3.52



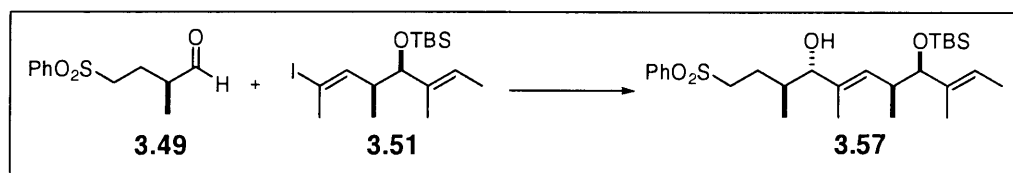
A solution of dibromide **3.56** (22.6 g, 54.9 mmol) in dry THF (300 mL) was cooled to  $-78^{\circ}\text{C}$ , and *n*-BuLi (2.5 M in hexanes, 48.3 mL, 120.8 mmol) was added dropwise over 30 min via syringe. The reaction mixture was then warmed to  $-20^{\circ}\text{C}$  and stirred for 1 h. The reaction mixture was then re-cooled to  $-78^{\circ}\text{C}$  and methyl iodide (17.1 mL, 274.5 mmol) was added in one portion. The reaction mixture was stirred at  $-78^{\circ}\text{C}$  for 10 min before warming to rt and quenching with saturated aqueous  $\text{NH}_4\text{Cl}$  solution (200 mL) and dilution with  $\text{Et}_2\text{O}$  (300 mL). The organic layer was separated and the aqueous layer extracted with  $\text{Et}_2\text{O}$  (2 x 200 mL). The combined organic extracts were dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The crude product was then purified by flash chromatography on silica gel, with neat hexanes as the eluent, to give 10.10 g (69%) of alkyne **3.52** as a clear oil. Data for **3.52**:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  5.39 (1H, m,  $\text{CH}_3\text{CH}=\text{C}$ ), 3.76 (1H, d,  $J = 7.7$  Hz,  $\text{CHOTBS}$ ), 2.45 (1H, m,  $\text{CH}(\text{CH}_3)\text{CHOTBS}$ ), 1.72 (3H, d,  $J = 2.4$  Hz,  $\text{CH}_3\text{CC}$ ), 1.58 (3H, dd,  $J = 6.7, 1.0$  Hz,  $\text{CH}_3\text{CH}=\text{C}$ ), 1.54 (3H, app t,  $J = 1.2$  Hz,  $\text{CH}_3\text{C}=\text{C}$ ), 1.10 (3H, d,  $J = 6.8$  Hz,  $\text{CH}_3\text{CHCHOTBS}$ ), 0.85 (9H, s,  $\text{SiC}(\text{CH}_3)_3$ ), 0.01 (3H, s,  $\text{SiCH}_3$ ), -0.06 (3H, s,  $\text{SiCH}_3$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  136.6, 121.4, 82.2, 81.9, 76.7, 31.5, 25.8, 18.2, 17.5, 12.9, 11.3, 3.5, -4.7, -5.1. HRMS (ESI) Calcd. for  $\text{C}_{16}\text{H}_{30}\text{OSi}$  ( $\text{M}+\text{Na}$ ) $^+$ : 289.19581. Found: 289.19574.

## Vinyl iodide 3.51



To a solution of alkyne **3.52** (250 mg, 0.94 mmol) in anhydrous THF (5 mL) at rt under N<sub>2</sub> was added bis(cyclopentadienyl)zirconium chloride hydride (Schwartz reagent) (485 mg, 1.88 mmol) in one portion. The reaction mixture was stirred at 60 °C for 1 h, then cooled to 0 °C and treated with I<sub>2</sub> (286 mg, 1.13 mmol). The reaction mixture was then gradually warmed to rt, and stirred at rt for 1 h. The reaction mixture was filtered through a short pad of silica, washed with neat hexanes. The filtrate was then concentrated in vacuo and purified by flash chromatography on silica gel to afford vinyl iodide **3.51** (230 mg, 62%) as a clear liquid. Data for **3.51**: [ $\alpha$ ]<sub>D</sub> +16.8 ° (c 1.0, CH<sub>2</sub>Cl<sub>2</sub>); IR (neat) cm<sup>-1</sup>: 2956 (s), 2929 (s), 2857 (s), 1467 (w), 1379 (w), 1253 (m), 1089 (s), 1044 (s), 836 (s), 774 (s); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  5.85 (1H, d, *J* = 10.2 Hz, CH<sub>3</sub>(I)C=CH), 5.31 (1H, q, *J* = 6.8 Hz, CH<sub>3</sub>CH=C), 3.64 (1H, d, *J* = 7.4 Hz, CHOTBS), 2.48 (1H, m, CH(CH<sub>3</sub>)CHOTBS), 2.32 (3H, d, *J* = 1.5 Hz, CH<sub>3</sub>(I)C=CH), 1.56 (3, dd, *J* = 6.7, CH<sub>3</sub>CH=C), 1.48 (3H, s, CH<sub>3</sub>C=C), 0.93 (3H, d, *J* = 6.8 Hz, CH<sub>3</sub>CHCHOTBS), 0.86 (9H, s, SiC(CH<sub>3</sub>)<sub>3</sub>), 0.00 (3H, s, SiCH<sub>3</sub>), -0.07 (3H, s, SiCH<sub>3</sub>); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  144.6, 136.5, 121.2, 92.7, 81.8, 40.6, 27.7, 25.8, 18.2, 16.3, 13.0, 11.5, -4.7, -5.2; HRMS (FAB+) Calcd. for C<sub>16</sub>H<sub>31</sub>IOSi (M+Na)<sup>+</sup>: 417.10865. Found: 417.10778.

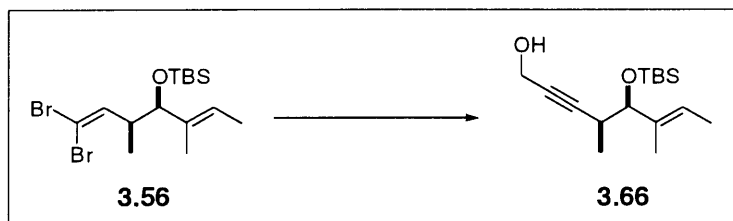
### Alcohol 3.57



Aldehyde **3.49** (344 mg, 1.52 mmol) was added neat to vinyl iodide **3.51** (500 mg, 1.27 mmol), and the mixture was azeotroped from benzene before being taken up into anhydrous DMSO (10 mL) under N<sub>2</sub>. CrCl<sub>2</sub> poisoned with 0.1% NiCl<sub>2</sub> (1.13 g CrCl<sub>2</sub>, 1.2 mg NiCl<sub>2</sub>, handled under N<sub>2</sub> atmosphere in a glove bag) was then added in one portion, and the resultant dark green solution was stirred at rt for 24 h. The reaction was then quenched by addition of saturated aqueous NH<sub>4</sub>Cl solution (10 ml) and the product was extracted with EtOAc (4 x 20 mL). The combined organic extracts were then dried (MgSO<sub>4</sub>), filtered and concentrated under reduced pressure. Purification by flash chromatography (gradient elution

10:1 to 5:1 petrol/EtOAc) furnished 231 mg (37%) of **3.57** as a thick oil, as well as 105 mg (17%) of the C(34) epimer, also as an oil. Data for **3.57**:  $[\alpha]_D^{+33.2}$  (c 1.04, CH<sub>2</sub>Cl<sub>2</sub>); IR (neat) cm<sup>-1</sup>: 3440 (br s), 2957 (s), 2928 (s), 2856 (m), 1447 (w), 1306 (w), 1146 (s), 1087 (s), 1051 (s), 836 (w), 774 (w); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  7.89 (2H, m, ArH), 7.63 (1H, m, ArH), 7.54 (2H, m, ArH), 5.24 (1H, q,  $J$  = 6.7 Hz, C=CHCH<sub>3</sub>), 5.01 (1H, d,  $J$  = 9.8 Hz, C=CHCH(CH<sub>3</sub>)), 3.61 (1H, d,  $J$  = 8.0 Hz, CHOTBS), 3.49 (1H, d,  $J$  = 8.8 Hz, CHOH), 3.19 (2H, m, PhSO<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 2.47 (1H, m, CH(CH<sub>3</sub>)CHOTBS), 2.00 (1H, m, PhSO<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 1.64-1.54 (2H, m, PhSO<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>, CH(CH<sub>3</sub>)CHOH), 1.51 (6H, m, CH<sub>3</sub>CH=C, CH<sub>3</sub>C=C), 1.45 (3H, s, CH<sub>3</sub>C=C), 0.89 (3H, d,  $J$  = 6.6 Hz, CH<sub>3</sub>CHCHOTBS), 0.85 (9H, s, (CH<sub>3</sub>)<sub>3</sub>C), 0.67 (3H, d,  $J$  = 6.8 Hz, CH<sub>3</sub>CHCHOH), -0.01 (3H, s, CH<sub>3</sub>Si), -0.08 (3H, s, CH<sub>3</sub>Si); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  139.3, 137.4, 134.6, 133.5, 132.2, 129.2, 128.1, 120.8, 82.9, 82.8, 54.6, 36.8, 34.9, 29.7, 26.3, 25.8, 18.2, 17.1, 16.2, 12.9, 11.20, 11.16, -4.7, -5.1; HRMS (FAB+) Calcd. for C<sub>27</sub>H<sub>46</sub>O<sub>4</sub>SSiNa (M+Na)<sup>+</sup>: 517.27836. Found: 517.27679.

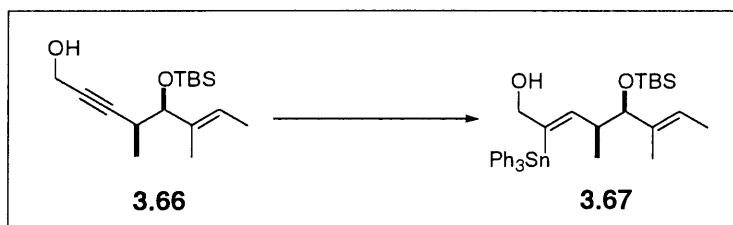
### Alkynol 3.66



To a solution of dibromoalkene **3.56** (2.05 g, 4.97 mmol) in dry THF (25 ml) at -78 °C under N<sub>2</sub> was added *n*-BuLi (2.5 M solution in hexanes, 4.37 ml, 10.93 mmol) dropwise over 4 min. The pale yellow solution was stirred at -78 °C for 0.5 h and allowed to warm to rt for a further 0.5 h. Solid paraformaldehyde (745 mg, 24.81 mmol) was added in one portion, and the reactants were stirred at rt for 16 h. H<sub>2</sub>O (30 ml) was then added and the mixture was extracted with Et<sub>2</sub>O (3 x 30 ml). The combined organic extracts were dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. The crude product was purified by SiO<sub>2</sub> flash chromatography (gradient elution with 50:1 then 20:1 then 10:1 petrol/EtOAc as eluent) to give **3.66** as a colourless liquid (552 mg, 39%). Data for **3.66**:  $[\alpha]_D^{+25.4}$  (c 0.87, CH<sub>2</sub>Cl<sub>2</sub>); IR

(neat) 3331 (br s, OH), 2984 (s), 2933 (s), 2858 (s), 2235 (w), 1674 (w), 1471 (s), 1464 (s), 1362 (s), 1296 (m), 1250 (s), 1217 (w), 1155 (m), 1070 (s), 1050 (s), 991 (s), 870 (s), 837 (s), 775 (s), 667(s), 561 (m);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  5.38 (apparent q 1H,  $J$  = 6.7 Hz,  $\text{CH}_3\text{CH}=\text{C}(\text{CH}_3)$ ), 4.15 (d, 2H,  $J$  = 2.1 Hz,  $\text{CH}_2\text{OH}$ ), 3.77 (d, 1H,  $J$  = 7.9 Hz,  $(\text{CH}_3)\text{CHCH}(\text{OTBS})$ ), 2.52 (m, 1H,  $(\text{CH}_3)\text{CHCH}(\text{OTBS})$ ), 2.00 (br s, 1H, OH), 1.56 (d, 3H,  $J$  = 6.7 Hz,  $\text{CH}_3\text{CH}=\text{C}(\text{CH}_3)$ ), 1.52 (s, 3H,  $\text{CH}_3\text{CH}=\text{C}(\text{CH}_3)$ ), 1.12 (d, 3H,  $J$  = 6.8 Hz,  $(\text{CH}_3)\text{CHCH}(\text{OTBS})$ ), 0.84 (s, 9H,  $(\text{CH}_3)_3\text{CSi}$ ), 0.00 (s, 3H,  $\text{CH}_3\text{Si}$ ), -0.07 (s, 3H,  $\text{CH}_3\text{Si}$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  136.3 ( $\text{CH}_3\text{CH}=\text{C}(\text{CH}_3)$ ), 122.0 ( $\text{CH}_3\text{CH}=\text{C}(\text{CH}_3)$ ), 88.6 ( $\text{CCH}_2\text{OH}$ ), 82.1 ( $\text{CH}(\text{OTBS})$ ), 79.8 ( $\text{CCH}_2\text{OH}$ ), 51.2 ( $\text{CH}_2\text{OH}$ ), 31.4 ( $(\text{CH}_3)\text{CHCH}(\text{OTBS})$ ), 25.7 ( $(\text{CH}_3)_3\text{CSi}$ ), 18.1 ( $(\text{CH}_3)_3\text{CSi}$ ), 17.2 ( $(\text{CH}_3)\text{CHCH}(\text{OTBS})$ ), 12.8 ( $\text{CH}_3\text{CH}=\text{C}(\text{CH}_3)$ ), 11.1 ( $\text{CH}_3\text{CH}=\text{C}(\text{CH}_3)$ ), -4.8 ( $\text{CH}_3\text{Si}$ ), -5.2 ( $\text{CH}_3\text{Si}$ ); HRMS(FAB+) Calcd. for  $\text{C}_{16}\text{H}_{30}\text{NaO}_2\text{Si}$  ( $\text{M}+\text{Na}$ ) $^+$ : 305.19127. Found: 305.19134.

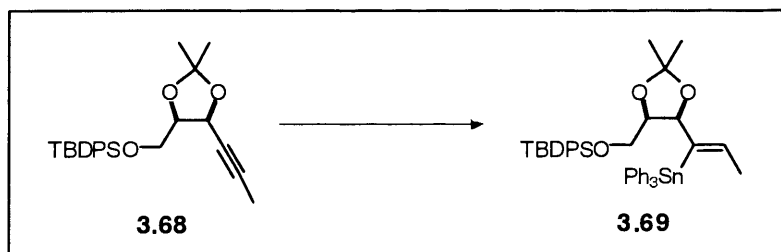
### Vinylstannane **3.67**



To a round-bottomed flask containing the alkynol **3.66** (50 mg, 0.177 mmol) was added  $\text{Ph}_3\text{SnH}$  (372 mg, 1.06 mmol). The flask was immediately purged with  $\text{N}_2$  and dry  $\text{PhMe}$  (1.77 ml) was added.  $\text{Et}_3\text{B}$  (0.0177 ml, 1 M solution in hexanes, 0.0177 mmol) was then added dropwise over 30 sec. Air (0.1 ml) was injected into the reaction vessel via a syringe, and the reactants were then stirred at rt for 5.5 h. After this time,  $\text{H}_2\text{O}$  (5 ml) was added, and the aqueous mixture was extracted with  $\text{EtOAc}$  (3 x 10 ml). The combined organic extracts were dried over  $\text{MgSO}_4$ , filtered, and concentrated *in vacuo*. Purification of the residue by  $\text{SiO}_2$  flash chromatography (gradient elution with 100:1-50:1-45:1 petrol/ $\text{EtOAc}$ ) gave 87 mg (78%) of the product as a colourless oil. Data for **3.67**:  $[\alpha]_{\text{D}}^{20} +30.4^\circ$  ( $c$  1.08,  $\text{CH}_2\text{Cl}_2$ ); IR (neat) 3576 (w), 3435 (br w), 3065 (m), 3047 (m), 2963 (s), 2931 (s), 2858 (s), 1622 (w), 1475 (w), 1454

(w), 1427 (s), 1369 (m), 1109 (s), 1070 (s), 1028 (s), 847 (w), 822 (w), 731 (s), 702 (s), 610 (w), 507 (m), 449 (s);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.63-7.61 (m, 2H, Ph), 7.60-7.48 (m, 6H, Ph), 7.42-7.28 (m, 12H, Ph), 6.16 (d, 1H,  $J = 10.1$  Hz,  $^3J^{119}\text{Sn}-^1\text{H} = 164.1$  Hz,  $^3J^{117}\text{Sn}-^1\text{H} = 156.5$  Hz,  $\text{CH}=\text{C}(\text{SnPh}_3)\text{CH}_2\text{OH}$ ), 5.10 (q, 1H,  $J = 6.8$  Hz,  $\text{CH}_3\text{CH}=\text{C}(\text{CH}_3)-$ ), 4.07 (dd, 1H,  $J = 6.0, 12.3$  Hz,  $\text{CH}_2\text{OH}$ ), 3.99 (dd, 1H,  $J = 4.4, 12.3$  Hz,  $\text{CH}_2\text{OH}$ ), 3.91 (d, 1H,  $J = 4.7$  Hz,  $\text{CHOTBDPS}$ ), 2.20 (m, 1H,  $\text{CH}_3\text{CHCHOTBDPS}$ ), 1.51 (br s,  $\text{CH}_2\text{OH}$ ), 1.32 (d, 3H,  $J = 6.6$  Hz,  $\text{CH}_3\text{CH}=\text{CCH}_3$ ), 1.01 (s, 9H,  $(\text{CH}_3)_3\text{CSi}$ ) 0.90 (s, 3H,  $\text{CH}_3\text{CH}=\text{CCH}_3$ ), 0.72 (d, 3H,  $J = 6.6$  Hz,  $\text{CH}_3\text{CHCHOTBDPS}$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  148.5 ( $\text{CH}=\text{C}(\text{SnPh}_3)\text{CH}_2\text{OH}$ ), 139.3 ( $\text{CH}=\text{C}(\text{SnPh}_3)\text{CH}_2\text{OH}$ ), 138.8, 137.1, 136.2, 136.1, 135.8 ( $\text{CH}_3\text{CH}=\text{CCH}_3$ ), 134.6, 134.4, 129.3, 128.8, 128.5, 127.3, 127.2, 120.9 ( $\text{CH}_3\text{CH}=\text{CCH}_3$ ), 81.3 ( $\text{CH}(\text{OTBDPS})$ ), 69.9 ( $\text{CH}_2\text{OH}$ ), 42.9 ( $(\text{CH}_3)\text{CHCH}(\text{OTBDPS})$ ), 27.2 ( $(\text{CH}_3)_3\text{CSi}$ ), 19.7 ( $(\text{CH}_3)_3\text{CSi}$ ), 15.6 ( $(\text{CH}_3)\text{CHCH}(\text{OTBDPS})$ ), 12.6 ( $\text{CH}_3\text{CH}=\text{CCH}_3$ ), 12.4 ( $\text{CH}_3\text{CH}=\text{CCH}_3$ ); HRMS(FAB+) Calcd. for  $\text{C}_{44}\text{H}_{50}\text{NaO}_2\text{SiSn}$  ( $\text{M}+\text{Na}$ ) $^+$ : 781.24996. Found: 781.24650.

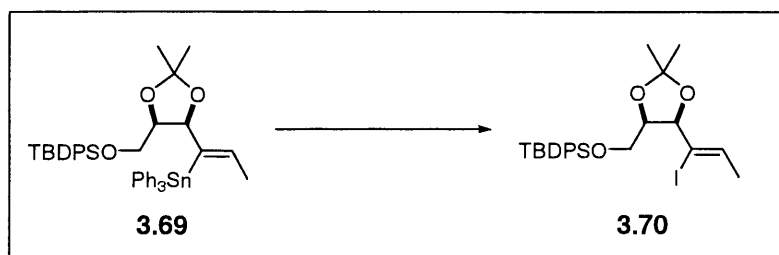
### Vinylstannane 3.69



Into a round-bottomed flask containing alkyne **3.68** (500 mg, 1.22 mmol) was added  $\text{Ph}_3\text{SnH}$  (640 mg, 1.83 mmol). The flask was immediately purged with  $\text{N}_2$  and dry PhMe (12.2 mL) was added.  $\text{Et}_3\text{B}$  (1 M solution in hexanes, 0.12 mL, 0.12 mmol) was then added dropwise over 30 sec. Air was then injected into the reaction vessel to initiate the reaction, and the reactants were stirred at rt for 16 h.  $\text{H}_2\text{O}$  was added and the mixture was extracted with EtOAc (x 3). The combined organic extracts were dried ( $\text{MgSO}_4$ ), filtered, and concentrated *in vacuo*. Purification of the residue by  $\text{SiO}_2$  flash chromatography (gradient elution with 150:1-100:1 petrol/EtOAc) gave 830 mg (88%) of the product **3.69** as a colourless oil. Data for **3.69**:  $[\alpha]_{\text{D}}$

+28.8 ° (c 0.89, CH<sub>2</sub>Cl<sub>2</sub>); IR (neat): 3046 (s), 2932 (s), 2857 (s), 1956 (w), 1890 (w), 1820 (w), 1728 (w), 1620 (m), 1588 (w), 1475 (s), 1428 (s), 1379 (s), 1244 (s), 1214 (s), 1168 (s), 1110 (s), 1074 (s), 893 (s), 855 (m), 824 (s), 793 (m), 730 (s), 706 (s), 613 (s), 509 (s). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 298K): 7.66-7.62 (m, 4H, Ph), 7.51-7.38 (m, 8H, Ph), 7.36-7.25 (m, 13H, Ph), 6.76 (qd, 1H, *J* = 1.6, 6.8 Hz, (<sup>3</sup>*J* <sup>119</sup>Sn-<sup>1</sup>H = 156.0 Hz, <sup>3</sup>*J* <sup>117</sup>Sn-<sup>1</sup>H = 149.2 Hz), CH<sub>3</sub>C(H)=C(SnPh<sub>3</sub>)-), 4.87 (dt, 1H, *J* = 1.4, 6.7 Hz, (<sup>3</sup>*J* <sup>119</sup>Sn-<sup>1</sup>H = 35.8 Hz, <sup>3</sup>*J* <sup>117</sup>Sn-<sup>1</sup>H = 34.2 Hz), -(O)CHC=CH(Me)), 3.97 (ddd, <sup>1</sup>H, *J* = 2.7, 2.7, 9.2 Hz, TBDPSOCH<sub>2</sub>CH(O-)-), 3.76 (dd, <sup>1</sup>H, *J* = 2.7, 10.8 Hz, TBDPSOCH<sub>2</sub>-), 3.56 (dd, 1H, *J* = 9.1, 10.8 Hz, TBDPSOCH<sub>2</sub>-), 1.69 (dd, 3H, *J* = 1.2, 6.8 Hz, CH<sub>3</sub>C(H)=C(SnPh<sub>3</sub>)-), 1.29 (s, 3H, (CH<sub>3</sub>)<sub>2</sub>C), 1.16 (s, 3H, (CH<sub>3</sub>)<sub>2</sub>C), 1.02 (9H, s, (CH<sub>3</sub>)<sub>3</sub>CSi); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>, 298K): 138.9 (CH<sub>3</sub>C(H)=C(SnPh<sub>3</sub>)-) 138.6 (CH<sub>3</sub>CH=CSnPh<sub>3</sub>), 136.9, 135.7, 135.6, 135.1, 133.9, 133.6, 129.5, 129.4, 128.8, 128.5, 127.6, 127.5 (Ar), 107.9 (CH<sub>3</sub>)<sub>2</sub>C, 81.3 (-(O)CH(Ph<sub>3</sub>Sn)C=CH(Me)), 79.3 (TBDPSOCH<sub>2</sub>CH(O-)-), 65.3 (TBDPSOCH<sub>2</sub>-), 27.3 and 25.6 ((CH<sub>3</sub>)<sub>2</sub>C), 26.8 ((CH<sub>3</sub>)<sub>3</sub>CSi), 20.9 (CH<sub>3</sub>C(H)=C(SnPh<sub>3</sub>)-), 19.2 ((CH<sub>3</sub>)<sub>3</sub>CSi); HRMS (ESP+) Calcd. for C<sub>43</sub>H<sub>48</sub>NaO<sub>3</sub>SiSn: (M+Na)+ 783.22869. Found: 783.22867.

### Vinyl iodide **3.70**

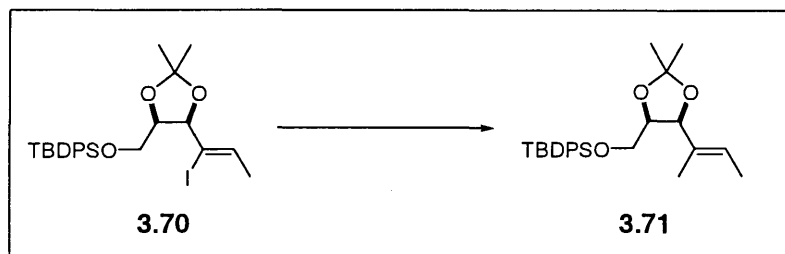


To a stirred solution of vinyl triphenylstannane **3.69** (410 mg, 0.53 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (5.4 mL) at -78 °C under N<sub>2</sub> was added solid I<sub>2</sub> (160 mg, 0.63 mmol) in one portion. The mixture was stirred at -78 °C for 10 min and then allowed to warm to rt where it was stirred for a further 20 min. H<sub>2</sub>O (20 mL) was added, and the two layers were separated. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 20 mL), and the combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated in vacuo. The crude residue was purified by SiO<sub>2</sub> flash chromatography with 150:1 petrol/EtOAc; the vinyl iodide **3.70** was isolated as a colourless oil



(270 mg, 93%). Data for **3.70**:  $[\alpha]_D -1.6^\circ$  (c 0.64,  $\text{CH}_2\text{Cl}_2$ ); IR (neat) 3048 (w), 2984 (w), 2933 (s), 2857 (m), 1589 (w), 1471 (w), 1428 (m), 1379 (m), 1243 (m), 1213 (m), 1111 (s), 1078 (s), 892 (w), 862 (w), 823 (w), 789 (w), 740 (m), 704 (s), 613 (w), 508 (m);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ , 298K)  $\delta$  7.69-7.64 (m, 4H, Ph), 7.43-7.34 (m, 6H, Ph), 6.08 (qd, 1H,  $J = 1.2, 6.5$  Hz,  $\text{CH}_3\text{C(H)=C(I)-}$ ), 4.75 (apparent d, 1H,  $J = 6.7$  Hz,  $-\text{CH(O-)}\text{C(I)=CH(Me)}$ ), 4.44 (dd, 1H,  $J = 6.2, 12.2$  Hz,  $\text{TBDPSOCH}_2\text{CH(O-)-}$ ), 3.84 (dd, 1H,  $J = 5.4, 11.0$  Hz,  $\text{TBDPSOCH}_2\text{-}$ ), 3.68 (dd, 1H,  $J = 6.1, 10.9$  Hz,  $\text{TBDPSOCH}_2\text{-}$ ), 1.74 (dd, 3H,  $J = 1.0, 6.5$  Hz,  $\text{CH}_3\text{C(H)=C(I)-}$ ), 1.52 (s, 3H,  $(\text{CH}_3)_2\text{C-}$ ), 1.36 (s, 3H,  $(\text{CH}_3)_2\text{C-}$ ), 1.04 (9H, s,  $(\text{CH}_3)_3\text{CSi(Ph)}_2\text{-}$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ , 298K)  $\delta$  135.7, 135.6, 133.5, 133.3 (Ph), 132.2 ( $\text{CH}_3\text{C(H)=C(I)-}$ ), 129.6, 127.6 (Ph), 109.0 ( $(\text{CH}_3)_2\text{C-}$ ), 103.0 ( $\text{CH}_3\text{C(H)=C(I)-}$ ), 82.7 ( $(-\text{O})\text{CHC(I)=CH(Me)}$ ), 78.7 ( $\text{TBDPSOCH}_2\text{CH(O-)-}$ ), 62.8 ( $\text{TBDPSOCH}_2\text{-}$ ), 27.1 and 25.4 ( $(\text{CH}_3)_2\text{C}$ ), 26.8 ( $(\text{CH}_3)_3\text{CSi}$ ), 21.4 ( $\text{CH}_3\text{C(H)=C(I)-}$ ), 19.2 ( $(\text{CH}_3)_3\text{CSi}$ ); HRMS (ESP+) Calcd. for  $\text{C}_{25}\text{H}_{33}\text{INaO}_3\text{Si}$ : (M+Na)+ 559.11359. Found: 559.11519.

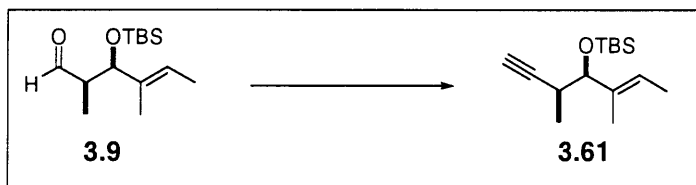
### Alkene 3.71



To a solution of vinyl iodide **3.70** (58 mg, 0.11 mmol) in dry DMF (1.1 mL) and freshly distilled  $\text{Et}_3\text{N}$  (1.1 mL, 7.89 mmol) at rt under  $\text{N}_2$  was added  $\text{Me}_4\text{Sn}$  (0.05 mL, 0.361 mmol),  $\text{CuI}$  (2 mg, 0.011 mmol), and  $\text{Ph}_3\text{As}$  (3.3 mg, 0.011 mmol) followed by  $(\text{CH}_3\text{CN})_2\text{PdCl}_2$  (2.8 mg, 0.011 mmol). The reactants were then heated at  $140^\circ\text{C}$  for 3 h, cooled to rt, and  $\text{H}_2\text{O}$  (5 mL) was added. After extraction with  $\text{Et}_2\text{O}$  (3 x 20 mL), the combined organic extracts were dried over  $\text{MgSO}_4$ , filtered, and concentrated in vacuo. Purification of the crude residue by  $\text{SiO}_2$  flash chromatography with 150:1 petrol/ $\text{EtOAc}$  as eluent afforded alkene **3.71** as a colorless oil (32 mg, 70%). Data for **3.71**:  $[\alpha]_D +3.7^\circ$  (c 0.38,  $\text{CH}_2\text{Cl}_2$ ); IR (neat) 3050 (w), 2932 (s), 2858 (s),

1469 (m), 1428 (m), 1380 (s), 1247 (m), 1214 (m), 1165 (m), 1111 (s), 1085 (s), 899 (w), 869 (w), 823 (m), 787 (w), 740 (m), 705 (s), 613 (w), 508 (w);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ , 298K):  $\delta$  7.67-7.60 (m, 4H, Ph), 7.42-7.33 (m, 6H, Ph), 5.58 (apparent qt, 1H,  $J = 1.2, 6.7$  Hz,  $\text{MeC(H)=C(Me)-}$ ), 4.54 (d, 1H,  $J = 6.5$  Hz,  $\text{-(O)CHC(Me)=CH(Me)}$ ), 4.30 (dd, 1H,  $J = 6.3, 12.1$  Hz,  $\text{TBDPSOCH}_2\text{CH(O-)-}$ ), 3.57 (dd, 1H,  $J = 6.4, 10.6$  Hz,  $\text{TBDPSOCH}_2\text{-}$ ), 3.50 (dd, 1H,  $J = 5.6, 10.6$  Hz,  $\text{TBDPSOCH}_2\text{-}$ ), 1.58 (d, 3H,  $J = 6.7$  Hz,  $\text{CH}_3\text{C(H)=C(CH}_3\text{)-}$ ) superimposed upon 1.57 (d, 3H,  $J = 1.2$  Hz,  $\text{CH}_3\text{C(H)=C(CH}_3\text{)-}$ ), 1.40 (s, 3H,  $(\text{CH}_3)_2\text{C}$ ), 1.34 (s, 3H,  $(\text{CH}_3)_2\text{C}$ ), 1.01 (9H, s,  $(\text{CH}_3)_3\text{CSiPh}_2$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ , 298K)  $\delta$  135.64, 135.55, 133.6, 133.3 (Ph), 130.9 ( $\text{CH}_3\text{C(H)=C(CH}_3\text{)-}$ ), 2 x 129.6, 2 x 127.6 (Ph), 121.4 ( $\text{CH}_3\text{CH=CCH}_3$ ), 107.7 ( $(\text{CH}_3)_2\text{C}$ ), 81.3 ( $\text{-(O)CHC(CH}_3\text{)=C(H)CH}_3$ ), 78.9 ( $\text{TBDPSOCH}_2\text{CH(O-)-}$ ), 63.3 ( $\text{TBDPSOCH}_2\text{-}$ ), 27.4 and 25.2 ( $(\text{CH}_3)_2\text{C}$ ), 26.8 ( $(\text{CH}_3)_3\text{CSiPh}_2$ ), 19.1 ( $(\text{CH}_3)_3\text{CSiPh}_2$ ), 14.2 ( $\text{CH}_3\text{C(H)=C(CH}_3\text{)-}$ ), 13.0 ( $\text{CH}_3\text{C(H)=C(CH}_3\text{)-}$ ); HRMS (ESP+): Calcd. For  $\text{C}_{26}\text{H}_{36}\text{NaO}_3\text{Si}$ :  $(\text{M}+\text{Na})^+$  447.23259. Found: 447.23172.

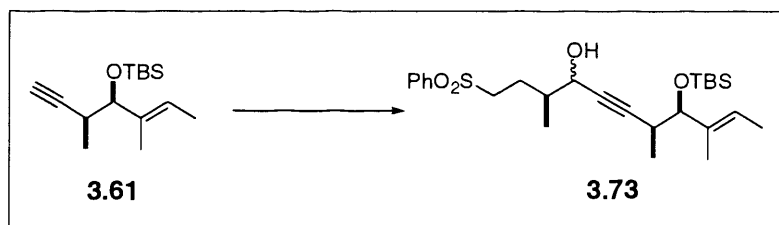
### Terminal acetylene **3.61**



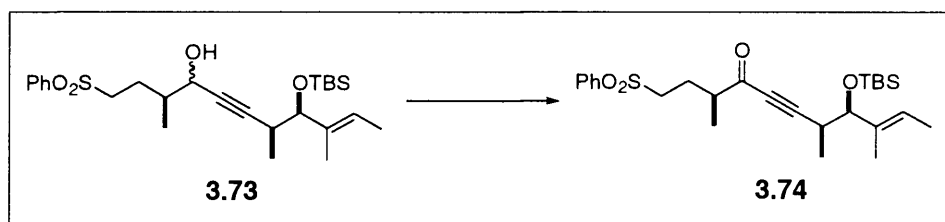
MeOH (50 ml) was added over 5 min to a flask containing a mixture of aldehyde **3.9** (3.90 g, 15.22 mmol),  $\text{K}_2\text{CO}_3$  (4.20 g, 30.4 mmol) and the Ohira-Bestmann reagent **3.72** (5.84 g, 30.4 mmol). The reactants were stirred at rt for 2 h and then quenched with sat. aq.  $\text{NH}_4\text{Cl}$  (50 ml). After stirring at rt for 10 min, the organic layer was separated, and the aqueous phase was extracted with EtOAc (2 x 200ml). The combined organic fractions were washed with  $\text{H}_2\text{O}$  (200 mL) and brine (200 mL), dried ( $\text{MgSO}_4$ ), filtered, and concentrated *in vacuo*. Purification of the residue by  $\text{SiO}_2$  flash chromatography (using 100:1 hexanes/EtOAc as eluent) gave the desired product **3.61** (3.0 g, 78%) as a runny, colourless, liquid. Data for **3.61**:  $[\alpha]_{\text{D}}^{+17.3}$  ( $c$  0.49,  $\text{CH}_2\text{Cl}_2$ ); IR (neat)  $\text{cm}^{-1}$ : 3314 (s), 2957 (s), 2930 (s), 2858 (m), 1472 (m), 1464 (m), 1258 (m), 1067 (s), 872 (m), 837 (s), 775 (s), 632 (m).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  5.41

(1H, q,  $J = 6.7$  Hz,  $\text{CH}_3\text{CH}=\text{C}(\text{CH}_3)$ ), 3.80 (1H, d,  $J = 8.1$  Hz,  $(\text{TBSO})\text{CHCH}(\text{CH}_3)$ ), 2.53 (1H, m,  $\text{HCCCH}(\text{CH}_3)\text{CH}(\text{OTBS})$ ), 1.97 (1H, d,  $J = 2.5$  Hz,  $\text{HCC}$ ), 1.59 (3H, d,  $J = 6.8$  Hz,  $\text{CH}_3\text{CH}=\text{C}(\text{CH}_3)$ ), 1.55 (3H, s,  $\text{CH}_3\text{C}=\text{CH}(\text{CH}_3)$ ), 1.17 (3H, d,  $J = 6.9$  Hz,  $(\text{CH}_3)\text{CHCCH}$ ), 0.86 (9H, s,  $\text{SiC}(\text{CH}_3)_3$ ), 0.02 (3H, s,  $\text{SiCH}_3$ ), -0.05 (3H, s,  $\text{SiCH}_3$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ , 298K):  $\delta$  136.2, 122.1, 86.9, 82.0, 69.4, 31.3, 25.8, 18.2, 17.4, 12.9, 11.0, -4.7, -5.1. HRMS ( $\text{Cl}^+$ ) Calcd. for  $\text{C}_{15}\text{H}_{29}\text{OSi}$  ( $\text{M}+\text{H}^+$ ): 253.19876, Found 253.19949.

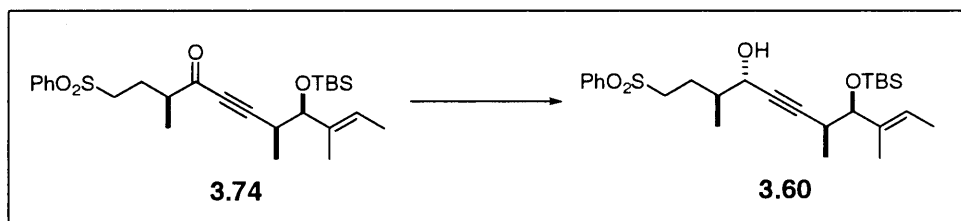
### Alkynol **3.73**



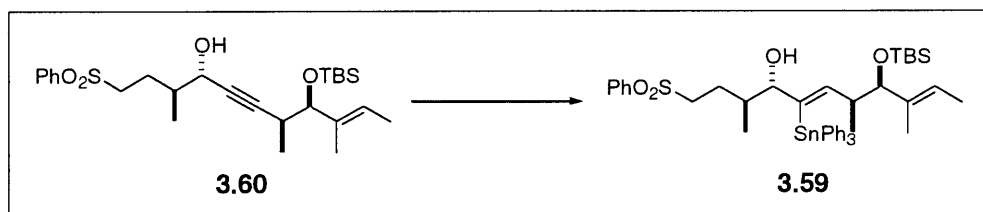
Alkyne **3.61** (1.00 g, 3.96 mmol) was dissolved in anhydrous THF (20 mL) and cooled to  $-30$  °C.  $n\text{-BuLi}$  (2.5 M in hexanes, 1.74 mL, 4.36 mmol) was added dropwise, and the resultant bright yellow solution was stirred at  $-30$  °C for 40 min. A solution of aldehyde **3.49** (0.94 g, 4.16 mmol) in THF (5 mL + 1 mL wash) was then added dropwise via syringe, and the reaction mixture was stirred at  $-30$  °C for 10 min before warming to rt. During the addition, the colour of the solution changed from yellow to colourless. The reaction mixture was quenched by addition of  $\text{H}_2\text{O}$  and the product was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo* to give an oil. Purification by  $\text{SiO}_2$  flash chromatography (gradient elution 10:1 to 5:1 petrol/EtOAc) gave 1.62 g (85%) of alkynol **3.73** as an oil which was a 1:1 mixture of C(34) epimers (as determined by  $^1\text{H}$  NMR).

Ynone **3.74**

To a round-bottomed flask containing approx. 1 g of activated 4 Å MS at rt under N<sub>2</sub> was added a solution of alkynol **3.73** (1.20 g, 2.51 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (20 mL). TPAP (88 mg, 0.25 mmol) and NMO (0.59 g, 5.20 mmol) were then added, and the reaction mixture was stirred at rt for 2 h. The mixture was then filtered through celite and the solvent was removed under reduced pressure. The crude material was then purified by SiO<sub>2</sub> flash chromatography (gradient elution 10:1 to 5:1 petrol/EtOAc) to give 892 mg (74%) of ynone **3.74** as a colourless oil. Data for **3.74**: IR (neat) cm<sup>-1</sup>: 2931 (s), 2857 (s), 2208 (s), 1670 (s), 1448 (m), 1309 (m), 1253 (m), 1149 (s), 1072 (s), 867 (s), 837 (s), 776 (s), 690 (m), 535 (m); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.87 (2H, m, ArH), 7.63 (1H, m, ArH), 7.54 (2H, m, ArH), 5.41 (1H, m, CH<sub>3</sub>CH=C(CH<sub>3</sub>)), 3.81 (1H, d, *J* = 8.2 Hz, CHOTBS), 3.04 (2H, m, PhSO<sub>2</sub>CH<sub>2</sub>), 2.69 (1H, m, CH(CH<sub>3</sub>)CHOTBS), 2.56 (1H, m, CH(CH<sub>3</sub>)C=O), 2.02 (1H, m, PhSO<sub>2</sub>CH<sub>2</sub>CHH), 1.82 (1H, m, PhSO<sub>2</sub>CH<sub>2</sub>CHH), 1.56 (3H, d, *J* = 6.7 Hz, CH<sub>3</sub>CH=C), 1.53 (3H, s, CH<sub>3</sub>C=C), 1.18 (3H, d, *J* = 6.9 Hz, CH<sub>3</sub>CHCHOTBS), 1.13 (3H, d, *J* = 7.1 Hz, CH<sub>3</sub>CHC=O), 0.84 (9H, s, SiC(CH<sub>3</sub>)<sub>3</sub>), 0.00 (3H, s, SiCH<sub>3</sub>), -0.06 (3H, s, SiCH<sub>3</sub>); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>, 298K): δ 189.8, 138.9, 136.0, 133.7, 129.3, 128.0, 122.8, 98.1, 81.4, 80.8, 53.7, 46.8, 31.9, 25.7, 24.9, 18.1, 16.6, 16.3, 12.9, 10.7, -4.7, -5.2; HRMS (FAB+) Calcd. for C<sub>15</sub>H<sub>29</sub>OSi (M+Na)<sup>+</sup>: 499.23141. Found 499.23156.

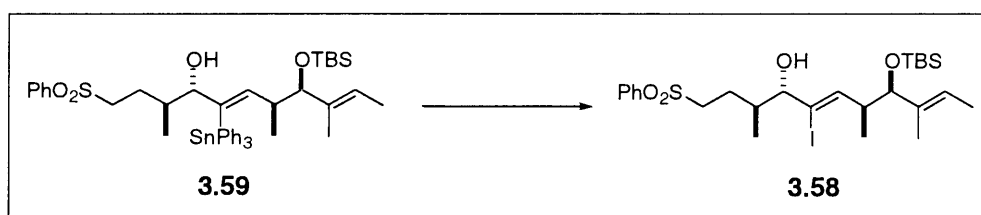
Alkynol **3.60**

Ynone **3.74** (500 mg, 1.05 mmol) was taken up in 10 mL of *i*-PrOH under N<sub>2</sub> at rt. The Noyori chiral ruthenium catalyst **3.75** (30 mg, 0.05 mmol) was then added, and the reaction mixture was stirred at rt for 1 h. The solvent was then removed under reduced pressure and the crude product was purified by SiO<sub>2</sub> flash chromatography (gradient elution 10:1 to 5:1 petrol/EtOAc) to furnish 365 mg (73%) of alkynol **3.60** as an oil which was a 5:1 mixture of C(34) epimers. Data for **3.60**: IR (neat) cm<sup>-1</sup>: 3494 (br m), 2931 (s), 2857 (s), 1448 (m), 1306 (m), 1253 (m), 1147 (s), 1054 (s), 871 (m), 837 (m), 776 (m), 690 (w), 535 (w); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.89 (2H, m, ArH), 7.64 (1H, m, ArH), 7.55 (2H, m, ArH), 5.34 (1H, q, *J* = 6.7 Hz, CH<sub>3</sub>CH=C), 4.08 (1H, dd, *J* = 5.8, 2.0 Hz, CHOH), 3.70 (1H, d, *J* = 8.5 Hz, CHOTBS), 3.13 (2H, m, PhSO<sub>2</sub>CH<sub>2</sub>), 2.51 (1H, m, CH(CH<sub>3</sub>)CHOTBS), 1.86 (1H, m, PhSO<sub>2</sub>CH<sub>2</sub>CHH), 1.70 (1H, m, CH(CH<sub>3</sub>)CHOH), 1.60 (1H, m, PhSO<sub>2</sub>CH<sub>2</sub>CHH), 1.54 (3H, dd, *J* = 6.7, 1.0 Hz, CH<sub>3</sub>CH=C), 1.49 (3H, app t, *J* = 1.2 Hz, CH<sub>3</sub>C=C), 1.11 (3H, d, *J* = 6.8 Hz, CH<sub>3</sub>CHCHOTBS), 0.90 (3H, d, *J* = 6.7 Hz, CH<sub>3</sub>CHCHOH), 0.84 (9H, s, SiC(CH<sub>3</sub>)<sub>3</sub>), 0.00 (3H, s, SiCH<sub>3</sub>), -0.07 (3H, s, SiCH<sub>3</sub>); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>, 298K): δ 139.2, 136.7, 133.6, 129.3, 128.1, 122.2, 89.3, 82.4, 66.5, 54.4, 38.4, 31.4, 25.8, 25.7, 18.2, 17.7, 15.2, 14.6, 12.9, 10.7, -4.7, -5.1; HRMS (FAB+) Calcd. for C<sub>26</sub>H<sub>42</sub>O<sub>4</sub>SSi (M+Na)<sup>+</sup>: 501.24706. Found 501.247867.

Vinylstannane **3.59**

To a round-bottomed flask containing the alkynol **3.60** (235 mg, 0.491 mmol) was added  $\text{Ph}_3\text{SnH}$  (482 mg, 1.374 mmol). The flask was immediately purged with  $\text{N}_2$  and dry  $\text{PhMe}$  (3 mL) was added.  $\text{Et}_3\text{B}$  (0.05 mL, 1 M solution in hexanes, 0.05 mmol) was then added dropwise. Air (0.1 mL) was injected into the reaction vessel via a syringe, and the reactants were then stirred at rt for 18 h. After this time,  $\text{H}_2\text{O}$  (5 mL) was added, and the aqueous mixture was extracted with  $\text{EtOAc}$  (3 x 10 mL). The combined organic extracts were dried over  $\text{MgSO}_4$ , filtered, and concentrated *in vacuo*. Purification by flash chromatography on silica gel (gradient elution, 100:1 to 20:1 petrol/ $\text{EtOAc}$ ) gave 249 mg (61%) of **3.59** as a colourless oil, though  $^1\text{H}$  NMR spectra showed some inseparable triphenylstannane impurities were still present. The still impure material was taken on to the iododestannylation step without further purification.

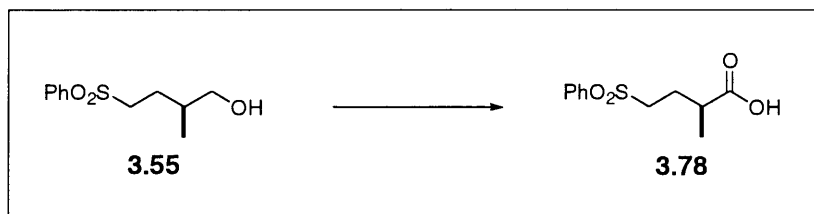
#### Vinyl iodide **3.58**



To a stirred solution of vinyl triphenylstannane **3.59** (950 mg, 1.14 mmol) in dry  $\text{CH}_2\text{Cl}_2$  at  $-78^\circ\text{C}$  was added solid  $\text{I}_2$  (0.40 g, 1.59 mmol) in one portion. The reaction mixture was stirred at  $-78^\circ\text{C}$  for 10 min, then warmed to room temperature and stirred for a further 1 h. The solvent was then removed *in vacuo* and the residue was purified by flash chromatography on  $\text{SiO}_2$  (gradient elution, 150:1 to 50:1 petrol/ $\text{EtOAc}$ ) to give vinyl iodide **3.58** (462 mg, 67%) as a colourless oil. Data for **3.58**:  $[\alpha]_{\text{D}} +19.8^\circ$  (c 0.18,  $\text{CH}_2\text{Cl}_2$ ); IR (neat)  $\text{cm}^{-1}$ : 3492 (br s), 2957 (s), 2928 (s), 2856 (m), 1448 (w), 1306 (w), 1146 (s), 1087 (s), 1058 (m), 836 (w), 775 (m);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.89 (2H, m,  $\text{ArH}$ ), 7.63 (1H, m,  $\text{ArH}$ ), 7.54 (2H, m,  $\text{ArH}$ ), 5.55 (1H, d,  $J = 9.1$  Hz,  $\text{CH}=\text{Cl}$ ), 5.30 (1H, q,  $J = 6.7$  Hz,  $\text{C}=\text{CHCH}_3$ ), 3.79 (1 H, d,  $J = 7.1$  Hz,  $\text{CHOTBS}$ ), 3.19 (2H, m,  $\text{PhSO}_2\text{CH}_2\text{CHH}$ ), 3.06 (1H, dd,  $J = 8.8, 5.5$  Hz,  $\text{CHOH}$ ), 2.57 (1H, m,  $\text{CH}(\text{CH}_3)\text{CHOTBS}$ ), 2.08 (1H, m,  $\text{PhSO}_2\text{CH}_2\text{CHH}$ ), 1.72 (1H, m,  $\text{CH}(\text{CH}_3)\text{CHOH}$ ), 1.64 (1H,

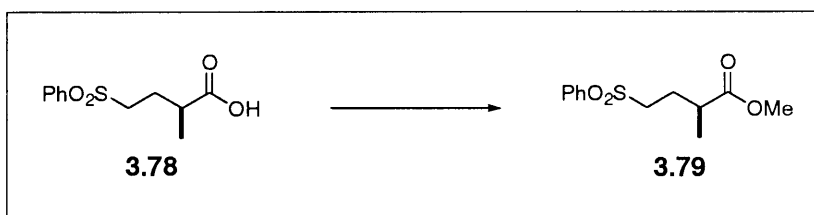
m,  $\text{PhSO}_2\text{CH}_2\text{CHH}$ ), 1.53 (3H, d,  $J = 6.8$  Hz,  $\text{CH}_3\text{CH}=\text{C}$ ), 1.50 (3H, s,  $\text{CH}_3\text{C}=\text{C}$ ), 0.92 (3H, d,  $J = 6.7$  Hz,  $\text{CH}_3\text{CHCHOTBS}$ ), 0.86 (9H, s,  $(\text{CH}_3)_3\text{C}$ ), 0.69 (3H, d,  $J = 6.7$  Hz,  $\text{CH}_3\text{CHCHOH}$ ), -0.02 (3H, s,  $\text{CH}_3\text{Si}$ ), -0.08 (3H, s,  $\text{CH}_3\text{Si}$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  141.2, 139.1, 136.9, 133.6, 129.2, 128.1, 121.0, 113.1, 82.6, 81.1, 54.6, 44.8, 37.4, 25.8, 25.5, 18.2, 16.1, 15.2, 12.9, 11.8, -4.7, -5.1; HRMS (FAB+) Calcd. for  $\text{C}_{26}\text{H}_{43}\text{IO}_4\text{SSiNa}$  ( $\text{M}+\text{Na}$ ) $^+$ : 629.15938. Found: 629.15857.

### Carboxylic acid **3.78**



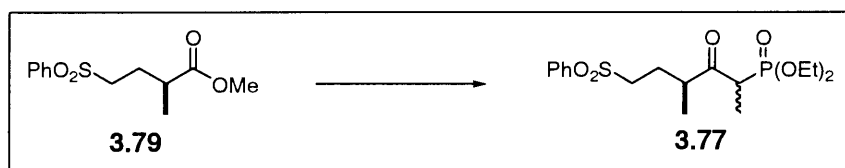
Alcohol **3.55** (5.00 g, 21.9 mmol) was dissolved in a mixture of  $\text{CCl}_4$  (20 mL) / MeCN (20 mL) /  $\text{H}_2\text{O}$  (30 mL) at rt.  $\text{NaIO}_4$  (9.85 g, 46.0 mmol) was added in 3 portions over 10 min, followed by  $\text{RuCl}_3$  (455 mg, 2.20 mmol) in 3 portions over 10 min. The reaction mixture was stirred at rt for 20 min, before dilution with 100 mL  $\text{CH}_2\text{Cl}_2$  and 50 mL  $\text{H}_2\text{O}$ . The organic layer was separated, and the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (2 x 100 mL). The combined organic extracts were dried over  $\text{MgSO}_4$  and then concentrated under reduced pressure to give crude acid **3.78**, which was used in the next step without further purification.

### Methyl ester **3.79**



To a solution of crude carboxylic acid **3.78** (< 21.9 mmol) in anhydrous DMF (80 mL) under N<sub>2</sub> at rt was added K<sub>2</sub>CO<sub>3</sub> (6.05 g, 43.8 mmol) and MeI (5.45 mL, 87.6 mmol). The reaction mixture was stirred at rt for 30 min, then quenched with saturated aqueous NH<sub>4</sub>Cl solution (50 mL) and extracted with Et<sub>2</sub>O (3 x 100 mL). The organic extracts were dried over MgSO<sub>4</sub>, filtered and concentrated in vacuo before purification by flash chromatography on silica gel (5:1 hexanes/EtOAc as eluent) to give 3.72 g (66% for 2 steps) of methyl ester **3.79** as a clear oil. NMR data for **3.79**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.86 (2H, m, ArH), 7.65 (1H, m, ArH), 7.54 (2H, m, ArH), 3.60 (3H, s, CO<sub>2</sub>CH<sub>3</sub>), 3.10 (2H, m, PhSO<sub>2</sub>CH<sub>2</sub>), 2.53 (1H, m, CH(CH<sub>3</sub>)CHO), 1.98 (1H, m, PhSO<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 1.84 (1H, m, PhSO<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 1.12 (3H, d, *J* = 7.1 Hz, CH<sub>3</sub>); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 175.3, 138.8, 133.7, 129.3, 128.0, 53.9, 51.8, 37.8, 26.1, 17.0, 6.2.

#### β-Ketophosphonate **3.77**

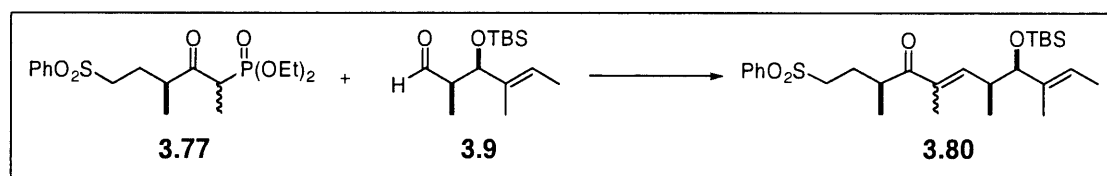


To a solution of diethyl ethylphosphonate (3.97 mL, 35.1 mmol) in anhydrous THF (35 mL) at -78 °C under N<sub>2</sub> was added *n*-BuLi (2.5 M in hexanes, 14.5 mL, 36.3 mmol) dropwise over 10 min. The reaction mixture was stirred at -78 °C for 25 min. A solution of methyl ester **3.79** (3.00 g, 11.7 mmol) in THF (15 mL + 5 mL wash) was added dropwise via syringe, and the reaction mixture was stirred for a further 20 min at -78 °C. The reaction was then quenched by addition of saturated aqueous NH<sub>4</sub>Cl solution (25 mL) and the product was extracted with EtOAc (3 x 100 mL). The combined organics were washed with H<sub>2</sub>O (x 5) to remove excess diethyl ethylphosphonate starting material and leave reasonably pure (as determined by <sup>1</sup>H NMR) β-ketophosphonate **3.77** (3.56 g, 78%) as a 1:1 mixture of diastereomers. Data for **3.77**: IR (neat) cm<sup>-1</sup>: 2982 (m), 1711 (s), 1448 (m), 1307 (s), 1245 (s), 1149 (s), 1023 (s), 963 (m), 745 (w), 691 (w), 535 (w); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.89-7.86 (2H, m, ArH), 7.66-7.61 (1H, m, ArH), 7.57-7.52 (2H, m, ArH), 4.12-4.01 (4H, m, 2 x CH<sub>2</sub>CH<sub>3</sub>), 3.39-3.27 (1H, m,



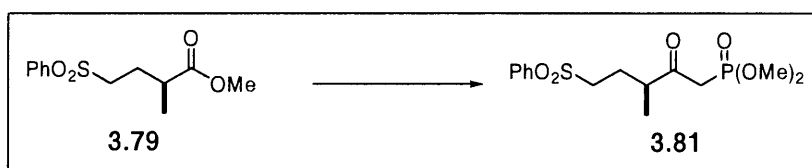
$\text{CH}(\text{CH}_3)\text{P}=\text{O}$ ), 3.13-2.98 (3H, m,  $\text{PhSO}_2\text{CH}_2$ ,  $\text{CH}(\text{CH}_3)\text{C}=\text{O}$ ), 2.06-1.98 (1H, m,  $\text{PhSO}_2\text{CH}_2\text{CHH}$ ), 1.79-1.69 (1H, m,  $\text{PhSO}_2\text{CH}_2\text{CHH}$ ), 1.31-1.25 (9H, m, 2 x  $\text{CH}_2\text{CH}_3$ ,  $\text{CH}_3\text{CHP}=\text{O}$ ), 1.07 (3H, 2 x superimposed doublets,  $J = 6.8$  Hz);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  208.0, 139.0, 138.9, 133.8, 133.6, 129.4, 129.2, 128.02, 127.95, 62.82, 62.79, 62.77, 62.73, 62.62, 62.57, 62.52, 53.79, 53.49, 45.5, 45.3, 44.5, 44.3, 25.6, 24.8, 17.2, 16.39, 16.38, 16.36, 16.34, 15.7, 11.4, 11.11, 11.07; HRMS (FAB+) Calcd. for  $\text{C}_{17}\text{H}_{27}\text{O}_6\text{PS}$  ( $\text{M} + \text{Na}$ ) $^+$ : 413.11636. Found: 413.11695.

### $\alpha,\beta$ -Unsaturated ketone **3.80**



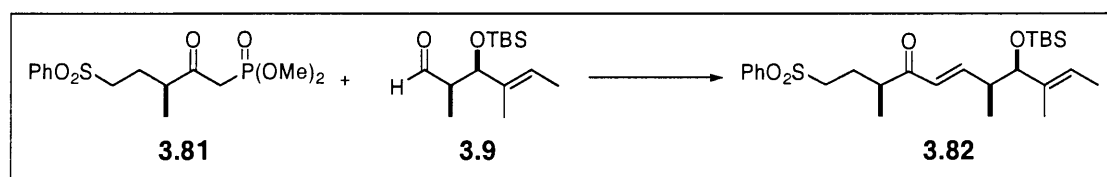
A mixture of  $\beta$ -ketophosphonate **3.77** (100 mg, 0.25 mmol) and  $\text{Ba}(\text{OH})_2 \cdot 8\text{H}_2\text{O}$  (60 mg, 0.20 mmol) in THF (0.5 mL) was stirred at rt for 30 min. A solution of aldehyde **3.9** (60 mg, 0.23 mmol) in 40:1 THF/ $\text{H}_2\text{O}$  (0.5 mL) was then added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 30 min, then warmed to rt and stirred for a further 30 min. The reaction mixture was then diluted with  $\text{CH}_2\text{Cl}_2$  (10 mL), washed with sat. aq.  $\text{NaHCO}_3$  solution and brine, dried over  $\text{MgSO}_4$  and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (petrol/EtOAc, 5:1) gave the product enone as a 2:1 mixture of stereoisomers (as determined by  $^1\text{H}$  NMR) that appeared as one spot on TLC.

### $\beta$ -Ketophosphonate **3.81**



To a solution of dimethyl methylphosphonate (0.38 mL, 3.51 mmol) in dry THF (4 mL) at -78 °C under N<sub>2</sub> atmosphere was added *n*-BuLi (2.5 M in hexane, 1.40 mL, 3.51 mmol) dropwise over 3 min. The reaction mixture was stirred at -78 °C for 30 min, and then a solution of methyl ester **3.79** (300 mg, 1.17 mmol) in THF (4 mL) was added dropwise by syringe over 5 min. The reaction mixture was stirred at -78 °C for 30 min, then quenched with saturated aqueous NH<sub>4</sub>Cl solution (5 mL) and extracted with EtOAc (3 x 10 mL). The combined organics were washed with H<sub>2</sub>O 5 times to remove excess dimethyl methylphosphonate starting material, then dried over MgSO<sub>4</sub> and concentrated under reduced pressure to give 460 mg (82%) of **3.81** as a thick oil. Data for **3.81**: IR (neat) cm<sup>-1</sup>: 3468 (br m), 2958 (m), 1712 (s), 1448 (s), 1258 (s), 1146 (s), 1031 (s), 811 (m), 736 (m), 691 (m), 535 (m); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.87-7.83 (2H, m, ArH), 7.65-7.61 (1H, m, ArH), 7.56-7.53 (2H, m, ArH), 3.74 (3H, d, *J* = 3.9 Hz, OCH<sub>3</sub>), 3.72 (3H, d, *J* = 3.9 Hz, OCH<sub>3</sub>), 3.22-2.91 (4H, m, PhSO<sub>2</sub>CH<sub>2</sub>, OCC<sub>2</sub>H<sub>2</sub>P(O)(OMe)<sub>2</sub>), 2.05-1.97 (1H, m, PhSO<sub>2</sub>CHH), 1.79-1.72 (1H, m, PhSO<sub>2</sub>CHH), 1.10 (3H, d, *J* = 7.1 Hz, CH<sub>3</sub>); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 204.0, 138.9, 133.7, 129.3, 127.9, 53.5, 53.0, 45.4, 40.2, 39.1, 24.8, 16.4; HRMS (FAB+) Calcd. for C<sub>26</sub>H<sub>42</sub>O<sub>4</sub>SSi (M + Na)<sup>+</sup>: 371.06941. Found: 371.06983.

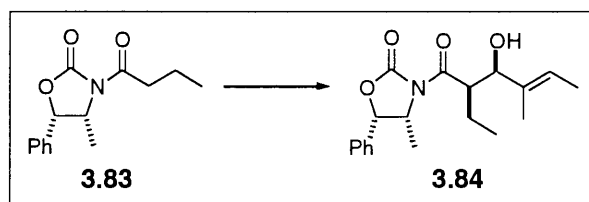
#### α,β-Unsaturated ketone **3.82**



A mixture of β-ketophosphonate **3.81** (100 mg, 0.29 mmol) and activated Ba(OH)<sub>2</sub>·8H<sub>2</sub>O (66 mg, 0.21 mmol) in THF (1 mL) was stirred at rt for 30 min. A solution of aldehyde **3.9** (67 mg, 0.26 mmol) in THF/H<sub>2</sub>O (40:1, 1 mL) was added, and the reaction mixture was stirred at rt for 5 h before dilution with CH<sub>2</sub>Cl<sub>2</sub> (25 mL) and washing with saturated NaHCO<sub>3</sub> solution (10 mL) and brine (10 mL). The organic solution was then dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was then purified by flash chromatography on silica gel (5:1 petrol/EtOAc as eluent) to furnish 93 mg (75%) of enone **3.82** as a colourless

oil. Data for **3.81**: IR (neat)  $\text{cm}^{-1}$ : 2957 (s), 2929 (s), 2856 (m), 1693 (m), 1668 (s), 1625 (m), 1448 (m), 1308 (m), 1149 (s), 1087 (s), 1055 (m), 837 (m), 775 (m);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ): 7.87 (2H, m, ArH), 7.63 (1H, m, ArH), 7.53 (2H, m, ArH), 6.64 (1H, dd,  $J = 15.9, 8.3$  Hz,  $\text{CH}=\text{CHCH}(\text{CH}_3)$ ), 5.96 (1H, dd,  $J = 15.9, 1.1$  Hz,  $\text{C}(\text{O})\text{CH}=\text{C}$ ), 5.32 (1H, q,  $J = 6.1$  Hz,  $\text{CH}_3\text{CH}=\text{C}$ ), 3.73 (1H, d,  $J = 7.7$  Hz,  $\text{CHOTBS}$ ), 3.07 (1H, m,  $\text{PhSO}_2\text{CHHCH}_2$ ), 2.96 (2H, m,  $\text{PhSO}_2\text{CHHCH}_2$ ,  $\text{CH}(\text{CH}_3)\text{C}=\text{O}$ ), 2.43 (1H, m,  $\text{C}=\text{CHCH}(\text{CH}_3)$ ), 2.00 (1H, m,  $\text{PhSO}_2\text{CH}_2\text{CHH}$ ), 1.79 (1H, m,  $\text{PhSO}_2\text{CH}_2\text{CHH}$ ), 1.51 (3H, dd,  $J = 6.7, 0.9$  Hz,  $\text{CH}_3\text{CH}=\text{C}$ ), 1.47 (3H, app t,  $J = 1.2$  Hz,  $\text{CH}_3\text{C}=\text{C}$ ), 1.04 (3H, d,  $J = 7.1$  Hz,  $\text{CH}_3\text{CHC}=\text{O}$ ), 1.02 (3H, d,  $J = 6.7$  Hz,  $\text{CH}_3\text{CHC}=\text{C}$ ), 0.85 (9H, s,  $(\text{CH}_3)_3\text{C}$ ), -0.01 (3H, s,  $\text{CH}_3\text{Si}$ ), -0.07 (3H, s,  $\text{CH}_3\text{Si}$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  202.1, 151.0, 139.1, 136.7, 133.7, 129.3, 128.0, 127.5, 121.7, 82.0, 53.9, 41.9, 41.5, 25.8, 25.3, 18.2, 17.4, 15.8, 12.8, 11.3, -4.7, -5.2; HRMS (FAB+) Calcd. for  $\text{C}_{26}\text{H}_{42}\text{O}_4\text{SSiNa}$  ( $\text{M} + \text{Na}$ ) $^+$ : 501.24706. Found: 501.24634.

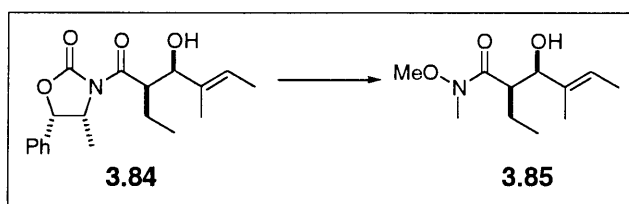
#### Aldol adduct **3.84**



To a cooled ( $-10\text{ }^{\circ}\text{C}$  -  $0\text{ }^{\circ}\text{C}$ ) and stirred solution of **3.83** (50.0 g, 202.4 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (800 mL) under  $\text{N}_2$  was successively added  $n\text{-Bu}_2\text{BOTf}$  (1 M solution in  $\text{CH}_2\text{Cl}_2$ , 226.7 mL, 226.7 mmol) dropwise over 2.5 h, followed by  $\text{Et}_3\text{N}$  (35.6 mL, 255.1 mmol) over 20 min. The internal reaction temperature was maintained below  $0\text{ }^{\circ}\text{C}$  during both additions. Stirring was continued for a further 45 min before the reaction mixture was cooled to  $-78\text{ }^{\circ}\text{C}$  and a solution of tiglic aldehyde (21.5 mL, 222.7 mmol) in  $\text{CH}_2\text{Cl}_2$  (200 mL) was added dropwise over 1.5 h. The reaction mixture was stirred at  $-78\text{ }^{\circ}\text{C}$  for a further 2 h before warming to rt and pouring into a 10% aq.  $\text{NaH}_2\text{PO}_4$  solution (700 mL). The organic phase was separated and the aqueous phase was extracted with  $\text{Et}_2\text{O}$  (3 x 800 mL). The combined organic extracts were

concentrated *in vacuo*, taken up in MeOH (800 mL), and cooled to 0 °C. A solution of 30% aq. H<sub>2</sub>O<sub>2</sub> and pH 7 aq. phosphate buffer (1:1, 400 mL) was added dropwise over 15 min to this mixture, and stirring was continued for a further 1 h at 0 °C until the brown colouration had been discharged. Excess peroxides were quenched with aq. FeSO<sub>4</sub> and the resulting brown solution was concentrated *in vacuo* to remove excess MeOH. The aqueous residue was extracted with Et<sub>2</sub>O (3 x 400 mL), and the combined organic extracts were washed successively with 5% aq. NaHCO<sub>3</sub> (200 mL) and brine (200 mL) before being dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo*. Purification of the residue by SiO<sub>2</sub> flash chromatography (gradient elution using 20:1-10:1-5:1 petrol/EtOAc as eluent) and crystallisation (Et<sub>2</sub>O/hexanes) of the resultant yellow oil gave 56.75 g (85%) of the desired aldol adduct **3.84** as a white crystalline solid. Data for **3.84**: [ $\alpha$ ]<sub>D</sub> +42.0 ° (c 0.267, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  7.42-7.34 (3H, m, Ph), 7.29-7.27 (m, 2H, Ph), 5.60 (1H, d, *J* = 7.2 Hz, PhCH(O)CH), 5.58 (1H, q, *J* = 1.3, 6.7 Hz, CH<sub>3</sub>CH=C(CH<sub>3</sub>)), 4.75 (1H, apparent quintet, NCH(CH<sub>3</sub>)CH(O)), 4.27 (1H, br d, *J* = 5.4 Hz, CH(OH)), 4.14 (m, 1H, CH(Et)CH(OH)), 2.35 (1H, br s, OH), 1.81-1.71 (2H, m, CH<sub>2</sub>CH<sub>3</sub>), 1.63-1.61 (6H, m, CH<sub>3</sub>CH=C, CH<sub>3</sub>CH=C), 0.91-0.86 (3H, m, CH<sub>3</sub>CH<sub>2</sub>, (CH<sub>3</sub>)CH(N)); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  175.7, 152.8, 134.9, 133.1, 128.8, 128.7, 125.6, 121.0, 78.8, 76.7, 55.1, 47.4, 20.3, 14.5, 13.1, 12.6, 11.5.

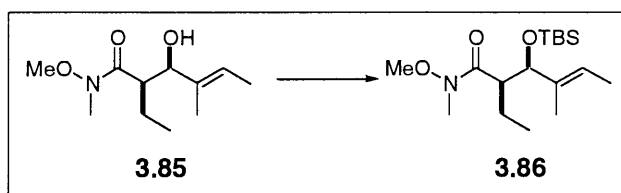
#### Weinreb amide **3.85**



To a suspension of MeNHOMe.HCl (21.01 g, 215.4 mmol) in anhydrous THF (150 mL) under N<sub>2</sub> at 0 °C was cautiously added Me<sub>3</sub>Al (2 M in hexanes, 107.7 mL, 215.4 mmol) dropwise via cannula over 40 min (CH<sub>4</sub> evolved; venting to bubbler is essential). The reaction mixture was stirred at 0 °C for 30 min, then at rt for 1.5 h, before re-cooling to -20 °C. A pre-cooled solution of **3.84** (23.80 g, 71.8 mmol) in THF (150 mL, 50 mL rinse) was then added via cannula and

the reactants were stirred at  $-20\text{ }^{\circ}\text{C}$  for 1.5 h. The reaction mixture was quenched by pouring it into a cooled ( $0\text{ }^{\circ}\text{C}$ ) solution of aq. HCl (1 M, 400 mL) and  $\text{CH}_2\text{Cl}_2$  (400 mL), and the resultant biphasic mixture was stirred vigorously for 1 h at  $0\text{ }^{\circ}\text{C}$ . The organic phase was separated and the aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 300 mL). The combined organic extracts were washed with  $\text{H}_2\text{O}$  (200 mL) and brine (200 mL), dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo*. The cleaved oxazolidinone was recovered by crystallisation ( $\text{Et}_2\text{O}$ /hexanes) from the resultant oil. The crude residue that remained was taken on without further purification. Data for **3.85**:  $[\alpha]_{\text{D}} -12.5\text{ }^{\circ}$  (*c* 1.22,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  5.58 (1H, qt,  $J = 6.8, 1.2\text{ Hz}$ ,  $\text{CH}_3\text{CH}=\text{C}$ ), 4.14 (1H, br d,  $J = 4.0\text{ Hz}$ ,  $\text{CHOH}$ ), 3.66 (3H, br s,  $\text{NOCH}_3$ ), 3.16 (3H, s,  $\text{NCH}_3$ ), 2.99 (1H, m,  $\text{CH}(\text{Et})\text{CHOH}$ ), 1.67 (2H, m,  $\text{CH}_3\text{CH}_2$ ), 1.58 (3H, d,  $J = 7.3\text{ Hz}$ ,  $\text{CH}_3\text{CH}=\text{C}$ ), 1.56 (3H, s,  $\text{CH}_3\text{CH}=\text{C}(\text{CH}_3)$ ), 0.83 (3H, t,  $J = 7.5\text{ Hz}$ ,  $\text{CH}_3\text{CH}_2$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  177.1, 134.1, 120.4, 76.1, 61.4, 44.6, 31.9, 19.2, 12.96, 12.92, 12.2. HRMS (FAB+) Calcd. for  $\text{C}_{11}\text{H}_{21}\text{NO}_3\text{Na}$  ( $\text{M}+\text{Na}$ ) $^{+}$ : 238.14191. Found: 238.14203.

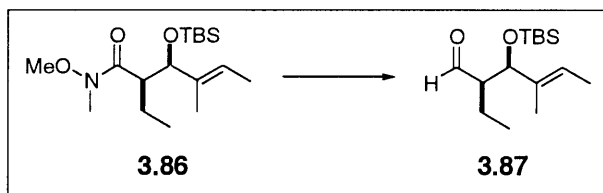
#### ***tert*-Butyldimethylsilyl Weinreb amide **3.86****



To a solution of Weinreb amide **3.85** (27.8 g, 129.1 mmol) in dry DMF (400 mL) under  $\text{N}_2$  was added TBSCl (38.9 g, 258.3 mmol) and imidazole (13.2 g, 193.7 mmol). The reaction mixture was stirred at room temperature for 4 h. The mixture was then diluted with  $\text{Et}_2\text{O}$  (300 mL) and saturated  $\text{NaHCO}_3$  solution (150 mL). The organic layer was separated, and the aqueous phase extracted with  $\text{Et}_2\text{O}$  (2 x 300 mL). The combined organics were washed with  $\text{H}_2\text{O}$  and brine, dried ( $\text{MgSO}_4$ ), and concentrated *in vacuo* to give a colourless oil. Purification by flash chromatography on silica gel (hexanes/ $\text{EtOAc}$ , 20:1 $\rightarrow$ 10:1) gave 38.5 g (90%) of the desired product as a clear, colourless oil. Data for **3.86**:  $[\alpha]_{\text{D}} +29.1\text{ }^{\circ}$  (*c* 1.28,  $\text{CH}_2\text{Cl}_2$ ); IR (neat)  $\text{cm}^{-1}$ :

2857 (s), 1664 (s), 1411 (s), 1382 (s), 1254 (s), 1067 (s), 1002 (s), 941 (m), 880 (m), 835 (m), 776 (m), 668 (w), 559 (w);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  5.29 (1H, q,  $\text{CH}_3\text{CH}=\text{C}$ ), 4.07 (1H, d,  $J = 9.5$  Hz,  $\text{CHOTBS}$ ), 3.61 (3H, s,  $\text{NOCH}_3$ ), 3.06 (3H, s,  $\text{NCH}_3$ ), 3.05 (1H, m,  $\text{CH}(\text{Et})\text{CHOTBS}$ ), 1.80 (1H, m,  $\text{CH}_3\text{CHH}$ ), 1.61 (1H, m,  $\text{CH}_3\text{CHH}$ ), 1.56 (3H, t,  $J = 1.1$  Hz,  $\text{CH}_3\text{C}=\text{C}$ ), 1.50 (3H, dd,  $J = 6.7, 0.9$  Hz,  $\text{CH}_3\text{CH}=\text{C}(\text{CH}_3)-$ ), 0.86 (9H, s,  $\text{SiC}(\text{CH}_3)_3$ ), 0.85 (3H, t,  $J = 7.5$  Hz,  $\text{CH}_3\text{CH}_2$ ), 0.02 (3H, s,  $\text{SiCH}_3$ ), -0.06 (3H, s,  $\text{SiCH}_3$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  175.8, 136.7, 121.1, 80.1, 61.4, 48.3, 32.2, 25.8, 22.6, 18.2, 12.9, 12.3, 11.0, -4.7, -5.1; HRMS (FAB+) Calcd. for  $\text{C}_{17}\text{H}_{35}\text{NO}_3\text{SiNa}$  ( $\text{M}+\text{Na}$ ) $^+$ : 352.22838. Found: 352.22787.

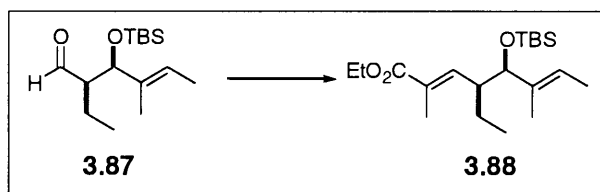
### Aldehyde 3.87



To a solution of **3.86** (38.3 g, 116.2 mmol) in dry PhMe (400 mL) under  $\text{N}_2$  at  $-20^\circ\text{C}$  was added DIBAL-H (1.5 M in PhMe, 85.2 mL, 127.8 mmol) dropwise over 1 h. The reaction mixture was stirred at  $-20^\circ\text{C}$  for a further 10 min before quenching by cautious dropwise addition of MeOH (50 mL) and pouring into a cooled ( $0^\circ\text{C}$ ) mixture of saturated Rochelle's salt solution (250 mL) and  $\text{Et}_2\text{O}$  (800 mL). This mixture was stirred vigorously at room temperature for 2 h before separation of the organic phase and extraction of the aqueous phase with  $\text{Et}_2\text{O}$  (2 x 250 mL). The combined organic extracts were washed sequentially with saturated Rochelle's salt solution (250 mL), saturated  $\text{NaHCO}_3$  solution (250 mL), and brine (250 mL), dried ( $\text{MgSO}_4$ ), and concentrated *in vacuo* to give a clear oil. Purification by flash chromatography on silica gel (hexanes/ $\text{EtOAc}$  as eluent, 100:1 $\rightarrow$ 50:1) gave 24.70 g (79%) of the aldehyde as a runny, colourless liquid, along with 6.50 g (17%) of recovered starting material. Data for **3.87**:  $[\alpha]_{\text{D}} +16.5^\circ$  ( $c$  0.52,  $\text{CH}_2\text{Cl}_2$ ); IR (neat)  $\text{cm}^{-1}$ : 2958 (s), 2932 (s), 2858 (s), 1724 (s), 1467 (m), 1385 (w), 1255 (s), 1060 (s), 837 (s), 776 (s), 673 (w);  $^1\text{H}$  NMR (500

MHz,  $\text{CDCl}_3$ ):  $\delta$  9.50 (1H, d,  $J = 3.6$  Hz,  $\text{CHO}$ ), 5.40 (1H, m,  $\text{CH}_3\text{CH}=\text{C}$ ), 4.22 (1H, d,  $J = 7.5$  Hz,  $\text{CHOTBS}$ ), 2.30 (1H, m,  $\text{CH}(\text{Et})\text{CHOTBS}$ ), 1.61 (3H, quintet,  $J = 7.0$  Hz,  $\text{CH}_2\text{CH}_3$ ), 1.54 (3H, d,  $J = 7.0$  Hz,  $\text{CH}_3\text{CH}=\text{C}$ ), 1.51 (3H, app t,  $J = 1.2$  Hz,  $\text{CH}_3\text{C}=\text{C}$ ), 0.85 (3H, t,  $J = 7.5$  Hz,  $\text{CH}_3\text{CH}_2$ ), 0.84 (9H, s,  $\text{Si}(\text{CH}_3)_3$ ), 0.00 (3H, s,  $\text{SiCH}_3$ ), -0.05 (3H, s,  $\text{SiCH}_3$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  204.4 (C-36), 136.0 (C-39), 122.0 (C-40), 77.8 (C-38), 58.4 (C-37), 25.7 ( $(\text{CH}_3)_3\text{C}$ ), 18.5 (C-46), 18.1 ( $(\text{CH}_3)_3\text{C}$ ), 12.9, 11.9, 11.5, -4.6 ( $\text{SiCH}_3$ ), -5.3 ( $\text{SiCH}_3$ ); HRMS (FAB+) Calcd. for  $\text{C}_{15}\text{H}_{30}\text{O}_2\text{SiNa}$  ( $\text{M}+\text{Na}$ ) $^+$ : 293.19127. Found: 293.19155.

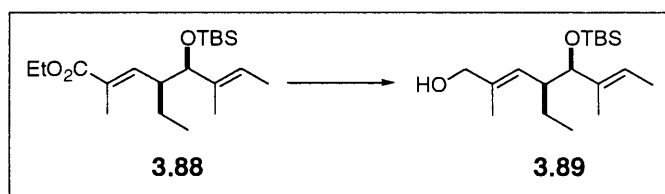
### $\alpha,\beta$ -Unsaturated ester **3.88**



To a solution of aldehyde **3.87** (24.6 g, 90.9 mmol) in anhydrous MeCN (350 mL) under  $\text{N}_2$  was added (carbethoxyethylidene)triphenylphosphorane (65.92 g, 181.9 mmol) in four portions. The reaction mixture was refluxed at  $80^\circ\text{C}$  for 48 h. The reaction mixture was then cooled to rt, and diluted with  $\text{H}_2\text{O}$  (200 mL) and EtOAc (400 mL). The organic phase was separated, and the aqueous layer was extracted with EtOAc (3 x 300 mL). The combined organics were washed with a saturated aqueous  $\text{NaHCO}_3$  solution (300 mL) and brine (300 mL), dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo* to give an orange slurry. Purification by  $\text{SiO}_2$  flash chromatography (gradient elution 100:1 to 20:1 petrol/EtOAc) gave 29.10 g (90%) of ester **3.88** as a clear oil. Data for **3.88**:  $[\alpha]_D^{+25.1}$  (c 0.73,  $\text{CH}_2\text{Cl}_2$ ); IR (neat)  $\text{cm}^{-1}$ : 2959 (s), 2931 (s), 2858 (s), 1714 (s), 1462 (m), 1367 (w), 1250 (s), 1093 (s), 1055 (s), 836 (s), 776 (s), 670 (w);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.39 (1H, d,  $J = 10.39$ ,  $\text{C}=\text{CHCH}(\text{Et})$ ), 5.31 (1H, q,  $J = 6.7$  Hz,  $\text{C}=\text{CHCH}_3$ ), 4.15 (2H, m,  $\text{CH}_3\text{CH}_2\text{O}$ ), 3.79 (1H, d,  $J = 7.5$  Hz,  $\text{CHOTBS}$ ), 2.44 (1H, m,  $\text{CH}(\text{Et})\text{CHOTBS}$ ), 1.79 (3H, d,  $J = 1.3$  Hz,  $\text{CH}_3(\text{CO}_2\text{Et})\text{C}=\text{C}$ ), 1.50 (3H, d,  $J = 6.8$  Hz,  $\text{CH}_3\text{CH}=\text{C}$ ), 1.46 (3H, s,  $\text{CH}_3\text{C}=\text{CHCH}_3$ ), 1.25 (3H, t,  $J = 4.7$  Hz,  $\text{CH}_3\text{CH}_2\text{OC}(\text{O})$ ), 0.86 (3H, d,  $J = 6.7$  Hz,  $\text{CH}_3\text{CHCHOTBS}$ ), 0.86 (9H, s,  $(\text{CH}_3)_3\text{C}$ ), 0.77 (3H, t,

$J = 7.5$  Hz,  $\text{CH}_3\text{CH}_2$ ), 0.00 (3H, s,  $\text{CH}_3\text{Si}$ ), -0.07 (3H, s,  $\text{CH}_3\text{Si}$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  168.3, 143.8, 136.8, 127.7, 121.1, 90.0, 60.3, 45.4, 25.9, 23.6, 18.2, 14.3, 12.85, 12.84, 11.6, 11.4, -4.7, -5.2; HRMS (FAB+) Calcd. for  $\text{C}_{20}\text{H}_{38}\text{O}_3\text{SiNa}$  ( $\text{M}+\text{Na}$ ) $^+$ : 377.24878, Found: 377.24809.

### Allylic alcohol **3.89**

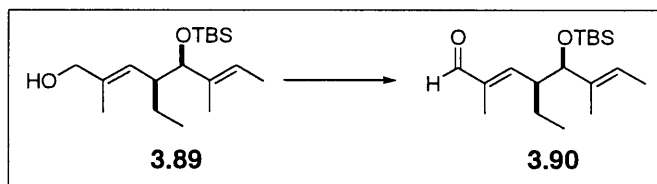


To a stirred solution of ester **3.88** (28.90 g, 81.5 mmol, azeotroped from toluene) in anhydrous  $\text{CH}_2\text{Cl}_2$  (450 mL) under  $\text{N}_2$  at  $-78^\circ\text{C}$  was added DIBAL-H (1.5 M in toluene, 114.1 mL, 171.2 mmol) over 30 min. The reaction mixture was stirred at  $-78^\circ\text{C}$  for 2 h before being quenched by careful dropwise addition of MeOH (30 mL). The resultant mixture was poured into a mixture of saturated Rochelle's salt solution (200 mL) and  $\text{Et}_2\text{O}$  (500 mL) at  $0^\circ\text{C}$ . This mixture was stirred at  $0^\circ\text{C}$  for 1 h and at rt for 1 h, at which point a clear separation between the organic and aqueous layers had been formed. The organic layer was then separated, and the aqueous layer was extracted with  $\text{Et}_2\text{O}$  (2 x 250 mL). The combined organics were washed with brine, dried over  $\text{MgSO}_4$  and concentrated *in vacuo* to give an oil. Purification by  $\text{SiO}_2$  flash chromatography (gradient elution 20:1 to 10:1 Petrol/ $\text{EtOAc}$ ) gave 21.20 g (83%) of alcohol **3.89** as a colourless oil. Data for **3.89**:  $[\alpha]_D^{25} +27.4^\circ$  ( $c$  0.56,  $\text{CH}_2\text{Cl}_2$ ); IR (neat)  $\text{cm}^{-1}$ : 3327 (br m), 2957 (s), 2930 (s), 2857 (s), 1460 (w), 1384 (w), 1252 (m), 1054 (s), 836 (s), 774 (m);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  5.23 (1H, q,  $J = 6.6$  Hz,  $\text{C}=\text{CHCH}_3$ ), 4.97 (1H, dd,  $J = 10.4$ , 1.0 Hz,  $\text{C}=\text{CHCH}(\text{CH}_3)$ ), 3.94 (2H, s,  $\text{CH}_2\text{OH}$ ), 3.69 (1H, d,  $J = 8.0$  Hz,  $\text{CHOTBS}$ ), 2.31 (1H, m,  $\text{CH}(\text{Et})\text{CHOTBS}$ ), 1.76 (1H, m,  $\text{CH}_3\text{CHH}$ ), 1.62 (3H, d,  $J = 1.1$  Hz,  $\text{CH}_3\text{C}(\text{CH}_2\text{OH})=\text{C}$ ), 1.51 (3H, d,  $J = 6.8$  Hz,  $\text{CH}_3\text{CH}=\text{C}$ ), 1.46 (3H, s,  $\text{CH}_3\text{C}=\text{CHCH}_3$ ), 1.28 (1H, br s, OH), 1.07 (1H, m,  $\text{CH}_3\text{CHH}$ ), 0.85 (9H, s,  $(\text{CH}_3)_3\text{C}$ ), 0.77 (3H, t,  $J = 7.5$  Hz,  $\text{CH}_3\text{CH}_2$ ), -0.01 (3H, s,  $\text{CH}_3\text{Si}$ ), -0.08 (3H, s,  $\text{CH}_3\text{Si}$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  137.5, 135.1, 128.2, 120.6, 81.8, 69.3, 44.0,

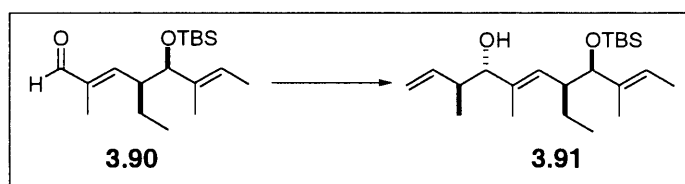


25.9, 24.1, 18.2, 14.2, 12.8, 11.5, 11.3, -4.6, -5.1; HRMS (FAB+) Calcd. for  $C_{18}H_{36}O_2SiNa$  ( $M+Na$ )<sup>+</sup>: 335.23821. Found: 335.23867.

### $\alpha,\beta$ -Unsaturated aldehyde **3.90**



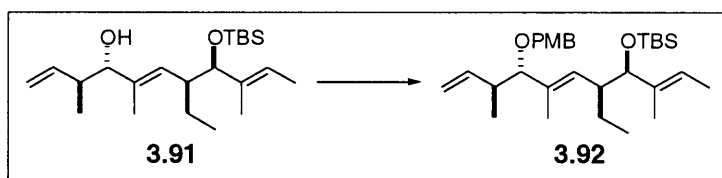
To a stirred solution of allylic alcohol **3.89** (20.90 g, 66.9 mmol) in  $CHCl_3$  (300 mL) was added  $MnO_2$  on activated carbon (58.13 g, 0.69 mol). The reaction mixture was heated at reflux at 60 °C for 3 h, and then cooled to rt and filtered through Celite (filter pad washed with excess  $CH_2Cl_2$ ). The filtrate was concentrated *in vacuo* and purified by  $SiO_2$  flash chromatography (gradient elution 50:1 to 20:1 Petrol/EtOAc) to give 17.84 g (86%) of aldehyde **3.90** as a colourless oil. Data for **3.90**:  $[\alpha]_D^{+68.8}$  (c 1.228,  $CH_2Cl_2$ ); IR (neat)  $cm^{-1}$ : 2958 (s), 2930 (s), 2857 (m), 1693 (s), 1644 (w), 1462 (w), 1253 (m), 1056 (s), 835 (s), 775 (m);  $^1H$  NMR (500 MHz,  $CDCl_3$ ):  $\delta$  9.32 (1H, s,  $\underline{CH}O$ ), 6.08 (1H, dq,  $J$  = 10.8, 1.3 Hz,  $CH_3C=CHCH(Et)$ ), 5.30 (1H, q,  $J$  = 6.7 Hz,  $C=CHCH_3$ ), 3.83 (1H, d,  $J$  = 8.0 Hz,  $\underline{CH}OTBS$ ), 2.66 (1H, m,  $\underline{CH}(Et)CHOTBS$ ), 1.88 (1H, m,  $\underline{CH}HCH_3$ ), 1.70 (3H, d,  $J$  = 1.3 Hz,  $\underline{CH}_3(CHO)C=C$ ), 1.49 (3H, d,  $J$  = 6.7 Hz,  $\underline{CH}_3CH=C$ ), 1.44 (3H, m,  $\underline{CH}_3C=CHCH_3$ ), 1.26 (1H, m,  $\underline{CH}HCH_3$ ), 0.86 (9H, s,  $(\underline{CH}_3)_3C$ ), 0.78 (3H, t,  $J$  = 7.6 Hz,  $\underline{CH}_3CH_2$ ), 0.00 (3H, s,  $\underline{CH}_3Si$ ), -0.07 (3H, s,  $\underline{CH}_3Si$ );  $^{13}C$  NMR (125 MHz,  $CDCl_3$ ):  $\delta$  195.5 (C-34), 156.2 (C-36), 139.5, 136.8, 121.6 (C-40), 81.0 (C-38), 45.7 (C-37), 25.8 ( $(\underline{CH}_3)_3CSi$ ), 24.0 (C-46), 18.2 ( $(CH_3)_3CSi$ ), 12.8, 11.5, 11.1, 9.7, -4.7 ( $\underline{SiCH}_3$ ), -5.2 ( $\underline{SiCH}_3$ ); HRMS (FAB+) Calcd. for  $C_{18}H_{34}O_2SiNa$  ( $M+Na$ )<sup>+</sup>: 333.22256. Found: 333.22205.

Allylic alcohol **3.91**

150 mL of an approximately 1 M solution of (*R,R*)-diisopropyl tartrate (*E*)-crotylboronate in toluene was prepared according to the procedure of Roush. 70 mL (70 mmol) of this freshly prepared solution was added to a flask containing 70 mL of anhydrous toluene and approximately 5 g of activated 4 Å molecular sieves under N<sub>2</sub> at rt. This mixture was stirred at rt for 30 min, and then cooled to -78 °C. A solution of aldehyde **3.90** (7.25 g, 23.3 mmol) in dry toluene (50 mL + 5 mL wash) was added dropwise via syringe over 1 h. The reaction mixture was stirred at -78 °C for a further 3 h, and then 70 mL of 2 M NaOH solution was added to hydrolyse DIPT. The reaction mixture was warmed to rt and stirred for 1 h, and then diluted with Et<sub>2</sub>O (200 mL) and filtered through celite. The organic layer was separated and the aqueous layer was extracted with Et<sub>2</sub>O (3 x 100 mL). The combined organics were washed with brine (200 mL), dried over anhydrous MgSO<sub>4</sub> and filtered. The filtrate was concentrated under reduced pressure and purified by silica gel flash chromatography (gradient elution 100:1 to 50:1 petrol/EtOAc) to give 5.30 g (62%) of product **3.91** as a colourless oil. Data for **3.91**: [α]<sub>D</sub> +44.2 ° (c 0.830, CH<sub>2</sub>Cl<sub>2</sub>); IR (neat) cm<sup>-1</sup>: 3476 (br m), 2957 (s), 2930 (s), 2858 (s), 1461 (w), 1381 (w), 1252 (m), 1053 (s), 836 (s), 774 (m), 670 (w); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 5.73 (1H, m, H<sub>2</sub>C=CH), 5.25 (1H, q, *J* = 6.1 Hz, C=CHCH<sub>3</sub>), 5.13-5.07 (2H, m, C=CH<sub>2</sub>), 4.97 (1H, d, *J* = 10.7 Hz, C=CHCH(Et)), 3.71 (1H, d, *J* = 8.1 Hz, CHOTBS), 3.62 (1H, d, *J* = 8.2 Hz, CHOH), 2.34 (2H, m, CH(Et)CHOTBS, CH(CH<sub>3</sub>)CHOH), 1.76 (1H, m, CHHCH<sub>3</sub>), 1.58 (3H, d, *J* = 1.3 Hz, CH<sub>3</sub>(CHOH)C=C), 1.52 (3H, dd, *J* = 6.7, 0.9 Hz, CH<sub>3</sub>CH=C), 1.47 (3H, s, CH<sub>3</sub>C=CHCH<sub>3</sub>), 1.09 (1H, m, CHHCH<sub>3</sub>), 0.89 (3H, d, *J* = 6.8 Hz, CH<sub>3</sub>CHCHOH), 0.86 (9H, s, (CH<sub>3</sub>)<sub>3</sub>C), 0.78 (3H, t, *J* = 7.5 Hz, CH<sub>3</sub>CH<sub>2</sub>), 0.00 (3H, s, CH<sub>3</sub>Si), -0.07 (3H, s, CH<sub>3</sub>Si); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 141.1, 137.6, 135.6, 130.2 (C-36), 120.7 (C-40), 115.8 (C-31), 81.8 (C-38), 81.4 (C-34), 44.0 (C-33/37), 41.6 (C-37/33), 25.9

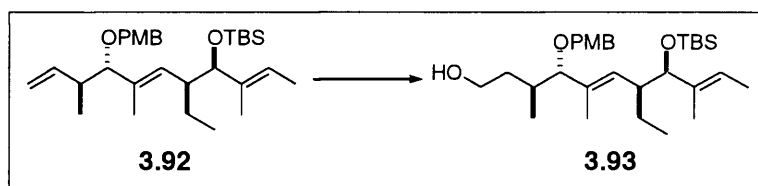
((CH<sub>3</sub>)<sub>3</sub>CSi), 24.1 (C-46) 18.2 ((CH<sub>3</sub>)<sub>3</sub>CSi), 16.6 (C-44), 12.8, 12.1, 11.6, 11.3, -4.7 (SiCH<sub>3</sub>), -5.1 (SiCH<sub>3</sub>); HRMS (FAB+) Calcd. for C<sub>22</sub>H<sub>42</sub>O<sub>2</sub>SiNa (M+Na)<sup>+</sup>: 389.28516. Found: 389.28585.

### PMB-ether **3.92**



To a solution of alcohol **3.91** (5.70 g, 15.5 mmol) and PMB-acetimidate (13.18 g, 46.6 mmol) in dry Et<sub>2</sub>O (80 mL) at 0 °C under N<sub>2</sub> was added TfOH (0.02 M solution in Et<sub>2</sub>O, 3.9 mL, 0.078 mmol) dropwise over 5 min. The reaction mixture was allowed to warm to rt and stirred for 3 h, then quenched with saturated aqueous NaHCO<sub>3</sub> solution (50 mL) and diluted with Et<sub>2</sub>O (300 mL). The organic layer was separated and the aqueous layer was extracted with Et<sub>2</sub>O (2 x 100 mL). The combined organics were washed with brine, dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. Purification by SiO<sub>2</sub> flash chromatography (gradient elution 100:1 to 50:1 petrol/EtOAc) gave 6.27 g (83%) of PMB-ether **3.92** as a colourless oil. Data for **3.92**: IR (neat) cm<sup>-1</sup>: 2927 (s), 2930 (s), 2857 (s), 1612 (m), 1512 (s), 1462 (m), 1383 (w), 1300 (m), 1248 (s), 1175 (m), 1054 (s), 870 (m), 835 (s), 775 (m), 671 (w), 577 (w); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.20 (2H, d, *J* = 8.4, ArH), 6.81 (2H, d, *J* = 8.4, ArH), 5.86 (1H, m, H<sub>2</sub>C=CH), 5.32 (1H, q, *J* = 6.7 Hz, C=CHCH<sub>3</sub>), 5.01 (1H, d, *J* = 17.3 Hz, C=CHH), 4.97 (1H, d, *J* = 10.4 Hz, C=CHH), 4.92 (1H, *J* = 10.4 Hz, C=CHCH(Et)), 4.26 (1H, d, *J* = 11.5 Hz, CHHAr), 3.98 (1H, d, *J* = 11.5 Hz, CHHAr), 3.75 (1H, d, *J* = 9.1 Hz, CHOTBS), 3.25 (1H, d, *J* = 9.4 Hz, CHOPMB), 2.48 (1H, m, CH(Et)CHOTBS), 2.38 (1H, m, CH(CH<sub>3</sub>)CHOPMB), 1.87 (1H, m, CHHCH<sub>3</sub>), 1.58 (3H, s, CH<sub>3</sub>(CHOPMB)C=C), 1.55 (3H, s, CH<sub>3</sub>C=CHCH<sub>3</sub>), 1.49 (3H, d, *J* = 6.7 Hz, CH<sub>3</sub>CH=C), 1.11 (1H, m, CHHCH<sub>3</sub>), 0.88 (9H, s, (CH<sub>3</sub>)<sub>3</sub>C), 0.86 (6H, m, CH<sub>3</sub>CHCHOH, CH<sub>3</sub>CH<sub>2</sub>), 0.04 (3H, s, CH<sub>3</sub>Si), -0.04 (3H, s, CH<sub>3</sub>Si); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 158.9, 157.9, 142.5, 138.2, 133.7, 133.3, 132.0, 129.3, 113.5, 113.3, 89.8, 82.5, 69.0, 55.2, 44.3, 40.1, 39.5, 25.9, 24.9, 18.2, 16.5, 13.1, 11.5, 11.3, 10.8, -4.6, -5.1.

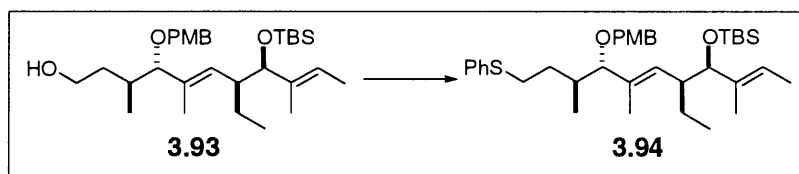
## Alcohol 3.93



To a solution of PMB-ether **3.92** (9.70 g, 19.9 mmol) in anhydrous THF (200 mL) under N<sub>2</sub> atmosphere at 0 °C was added a 0.5 M solution of 9-BBN in THF (79.7 mL, 39.85 mmol) dropwise over 30 min. The reaction mixture was stirred at 0 °C for 10 min, then allowed to warm to ambient temperature and stirred at rt for 2 h. The reaction mixture was then re-cooled to 0 °C, and a pre-mixed solution of 2M aq. NaOH (80 mL) and 30% aq. H<sub>2</sub>O<sub>2</sub> (80 mL) was carefully added. The resultant mixture was warmed to rt and stirred at this temperature for 2 h. Brine (100 mL) and Et<sub>2</sub>O (200 mL) were added, and the organic layer was separated. The aqueous phase was extracted with Et<sub>2</sub>O (3 x 100 mL), and the combined organics were dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. Purification by SiO<sub>2</sub> flash chromatography (gradient elution 10:1 to 5:1 petrol/EtOAc) gave 8.65 g (86%) of alcohol **3.93** as a clear, viscous oil. Data for **3.93**:  $[\alpha]_D^{+16.3}$  (c 0.814, CH<sub>2</sub>Cl<sub>2</sub>); IR (neat) cm<sup>-1</sup>: 3363 (br m), 2958 (s), 2929 (s), 2857 (s), 1612 (m), 1515 (s), 1462 (m), 1379 (w), 1301 (w), 1249 (s), 1173 (w), 1054 (s), 875 (m), 836 (s), 774 (m), 668 (w); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.18 (2H, d, *J* = 8.4 Hz, ArH), 6.84 (2H, d, *J* = 8.4 Hz, ArH), 5.29 (1H, q, *J* = 6.7 Hz, C=CHCH<sub>3</sub>), 4.93 (1H, d, *J* = 10.5 Hz, C=CHCH<sub>2</sub>Et), 4.24 (1H, d, *J* = 11.0 Hz, OCHHAr), 3.95 (1H, d, *J* = 11.0 Hz, OCHHAr), 3.77 (3H, s, ArOCH<sub>3</sub>), 3.74 (1H, d, *J* = 9.0 Hz, CHOTBS), 3.63 (1H, m, CHHOH), 3.53 (1H, m, CHHOH), 3.22 (1H, d, *J* = 9.3 Hz, CHOPMB), 2.48 (1H, app qd, *J* = 10.3, 3.0 Hz, CH(Et)CHOTBS), 2.28 (1H, br s, OH), 1.85 (1H, m, CHHCH<sub>3</sub>), 1.79 (1H, m, CH(CH<sub>3</sub>)CHOPMB), 1.72 (1H, m, CHHCH<sub>2</sub>OH), 1.56 (3H, d, *J* = 1.2 Hz, CH<sub>3</sub>C=C), 1.52 (3H, s, CH<sub>3</sub>C=C), 1.46 (1H, m, CHHCH<sub>2</sub>OH), 1.42 (3H, d, *J* = 6.7 Hz, CH<sub>3</sub>CH=C), 1.09 (1H, m, CHHCH<sub>3</sub>), 0.86 (9H, s, (CH<sub>3</sub>)<sub>3</sub>C), 0.82 (3H, t, *J* = 7.5 Hz, CH<sub>3</sub>CH<sub>2</sub>), 0.76 (3H, d, *J* = 6.8 Hz, CH<sub>3</sub>CHCHOPMB), 0.02 (3H, s, CH<sub>3</sub>Si), -0.06 (3H, s, CH<sub>3</sub>Si); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 159.2, 138.2, 133.6, 132.7 (C-36), 130.4, 129.8 (Ar C), 121.3 (C-40), 113.8 (Ar C), 91.0 (C-

34), 82.5 (C-38), 69.2 (OCH<sub>2</sub>Ar), 61.6 (C-31), 55.2 (ArOCH<sub>3</sub>), 44.4 (C-37), 38.0 (C-32), 33.2 (C-33), 25.9 ((CH<sub>3</sub>)<sub>3</sub>C), 24.9 (C-46), 18.2 ((CH<sub>3</sub>)<sub>3</sub>CSi), 17.9 (C-44), 13.0 (C-41), 11.5 (C-47), 11.1 (C-45/48), 10.8 (C-48/45), -4.6 (SiCH<sub>3</sub>), -5.1 (SiCH<sub>3</sub>); HRMS (FAB+) Calcd. for C<sub>30</sub>H<sub>52</sub>O<sub>4</sub>SiNa (M+Na)<sup>+</sup>: 527.35324. Found: 527.35395.

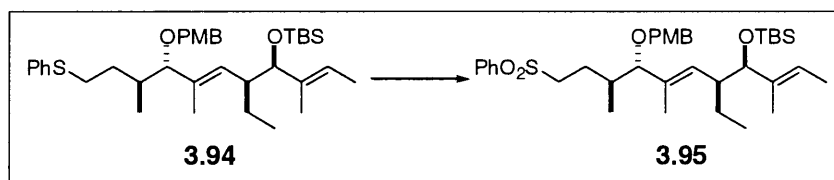
### Thioether 3.94



To a stirred solution of alcohol **3.93** (4.60 g, 9.1 mmol) in anhydrous DMF (50 mL) under N<sub>2</sub> atmosphere at rt was added diphenyldisulfide (3.97 g, 18.2 mmol) in one portion and tri-*n*-butylphosphine (5.23 mL, 21.0 mmol) dropwise over 10 min. The reaction mixture was stirred at rt for 2 h, and then quenched by addition of H<sub>2</sub>O (40 mL) and diluted with Et<sub>2</sub>O (250 mL). The organic layer was separated, and the aqueous layer was extracted with Et<sub>2</sub>O (2 x 100 mL). The combined organic extracts were then washed with brine, dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by SiO<sub>2</sub> flash chromatography (gradient elution 50:1 to 20:1 petrol/EtOAc) to give 4.75 g (87%) of thioether **3.94** as a clear oil. Data for **3.94**: [ $\alpha$ ]<sub>D</sub> +8.1 ° (*c* 0.988, CH<sub>2</sub>Cl<sub>2</sub>); IR (neat) cm<sup>-1</sup>: 2957 (s), 2929 (s), 2856 (s), 1612 (w), 1585 (w), 1513 (s), 1462 (m), 1379 (w), 1301 (w), 1249 (s), 1173 (w), 1054 (s), 874 (m), 836 (m), 775 (m), 738 (m), 691 (w), 668 (w); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  7.27-7.11 (7H, m, ArH), 6.81 (2H, m, ArH), 5.30 (1H, q, *J* = 5.7 Hz, C=CHCH<sub>3</sub>), 4.90 (1H, d, *J* = 10.5 Hz, C=CHCH<sub>2</sub>Et), 4.21 (1H, d, *J* = 11.3 Hz, OCH<sub>2</sub>HA<sub>r</sub>), 3.93 (1H, d, *J* = 11.3 Hz, OCH<sub>2</sub>HA<sub>r</sub>), 3.77 (3H, s, ArOCH<sub>3</sub>), 3.74 (1H, d, *J* = 9.0 Hz, CHOTBS), 3.16 (1H, d, *J* = 9.6 Hz, CHOPMB), 2.85 (2H, m, PhSCH<sub>2</sub>CH<sub>2</sub>), 2.47 (1H, app qd, *J* = 10.1, 2.9 Hz, CH(Et)CHOTBS), 2.02 (1H, m, PhSCH<sub>2</sub>CH<sub>2</sub>), 1.85 (1H, m, CHHCH<sub>3</sub>), 1.78 (1H, m, CH(CH<sub>3</sub>)CHOPMB), 1.54 (3H, d, *J* = 1.1 Hz, CH<sub>3</sub>C=C), 1.53 (3H, s, CH<sub>3</sub>C=C), 1.46 (3H, d, *J* = 6.7 Hz, CH<sub>3</sub>C=C), 1.43 (1H, m, PhSCH<sub>2</sub>CH<sub>2</sub>), 1.09 (1H, m, CHHCH<sub>3</sub>), 0.87 (9H, s, (CH<sub>3</sub>)<sub>3</sub>C), 0.82 (3H, t, *J* = 7.4 Hz, CH<sub>3</sub>CH<sub>2</sub>), 0.75 (3H, d, *J* = 6.9 Hz, CH<sub>3</sub>CHCHOPMB), 0.03 (3H, s, CH<sub>3</sub>Si), -0.05 (3H, s,

$\text{CH}_3\text{Si}$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  158.9, 138.2, 137.2, 133.7, 132.4 (C-36), 131.1, 129.6 (Ar C), 129.5 (Ar C), 128.75 (Ar C), 128.72 (Ar C), 125.4 (Ar C), 121.2 (C-40), 113.7 (Ar C), 90.0 (C-34), 82.5 (C-38), 69.0 ( $\text{OCH}_2\text{Ar}$ ), 55.2 ( $\text{ArOCH}_3$ ), 44.3 (C-37), 34.6, 33.2 (C-32), 31.1 (C-31), 25.9 ( $(\text{CH}_3)_3\text{C}$ ), 24.9 (C-46), 18.2 ( $(\text{CH}_3)_3\text{CSi}$ ), 16.2 (C-44), 13.1 (C-41), 11.6 (C-47), 11.2 (C-45/48), 10.8 (C-48/45), -4.6 ( $\text{SiCH}_3$ ), -5.1 ( $\text{SiCH}_3$ ). HRMS (FAB+) Calcd. for  $\text{C}_{36}\text{H}_{56}\text{O}_3\text{SSiNa}$  ( $\text{M}+\text{Na}$ ) $^+$ : 619.36169. Found: 619.35978.

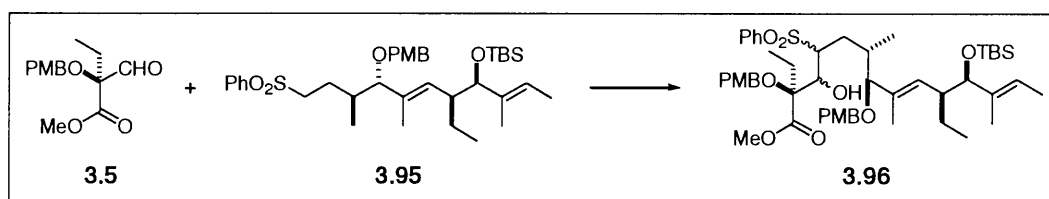
### Phenylsulfone **3.95**



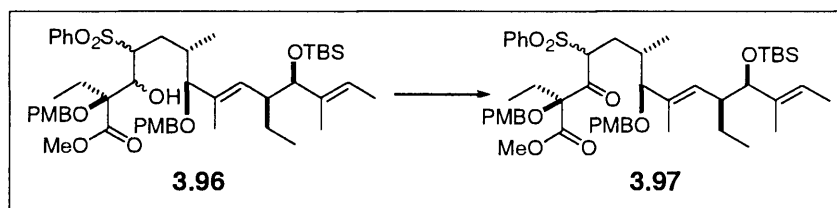
To a stirred solution of thioether **3.94** (6.46 g, 10.8 mmol) in THF/MeOH/ $\text{H}_2\text{O}$  (1:1:1, 105 mL) was added Oxone (19.96 g, 32.5 mmol) in 3 portions at rt. The reaction mixture was stirred vigorously at rt for 2 h, then diluted with EtOAc (250 mL) and  $\text{H}_2\text{O}$  (50 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organics were washed with brine, dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo*. Purification by  $\text{SiO}_2$  flash chromatography (gradient elution 10:1 to 8:1 petrol/EtOAc) gave 5.15 g (76 %) of phenylsulfone **3.95** as a thick, colourless oil. Data for **3.95**:  $[\alpha]_{\text{D}}^{20} +31.4^\circ$  ( $c$  0.758,  $\text{CH}_2\text{Cl}_2$ ); IR (neat)  $\text{cm}^{-1}$ : 2957 (s), 2930 (s), 2856 (s), 1612 (m), 1585 (w), 1514 (s), 1462 (m), 1447 (m), 1381 (w), 1304 (s), 1249 (s), 1147 (s), 1054 (s), 875 (m), 836 (m), 775 (m), 690 (w), 575 (w), 538 (w);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.81 (2H, m, ArH), 7.60 (1H, m, ArH), 7.49 (2H, m, ArH), 7.07 (2H, m, ArH), 6.83 (2H, m, ArH), 5.29 (1H, q,  $J$  = 6.5 Hz,  $\text{C}=\text{CHCH}_3$ ), 4.87 (1H, d,  $J$  = 10.5 Hz,  $\text{C}=\text{CHCH}_2\text{Et}$ ), 4.14 (1H, d,  $J$  = 11.1 Hz,  $\text{OCH}_2\text{HAr}$ ), 3.85 (1H, d,  $J$  = 11.2 Hz,  $\text{OCH}_2\text{HAr}$ ), 3.80 (3H, s,  $\text{ArOCH}_3$ ), 3.72 (1H, d,  $J$  = 9.0 Hz,  $\text{CHOTBS}$ ), 3.11 (1H, m,  $\text{PhSO}_2\text{CH}_2\text{CH}_2$ ), 3.08 (1H, d,  $J$  = 9.9 Hz,  $\text{CHOPMB}$ ), 2.99 (1H, m,  $\text{PhSO}_2\text{CH}_2\text{CH}_2$ ), 2.44 (1H, app qd,  $J$  = 9.6, 3.1 Hz,  $\text{CH}(\text{Et})\text{CHOTBS}$ ), 1.94 (1H, m,  $\text{PhSO}_2\text{CH}_2\text{CH}_2$ ), 1.84 (1H, m,  $\text{CH}_2\text{CH}_3$ ), 1.68 (1H, m,  $\text{CH}(\text{CH}_3)\text{CHOPMB}$ ), 1.57 (1H, m,  $\text{PhSO}_2\text{CH}_2\text{CH}_2$ ), 1.51 (3H, s,  $\text{CH}_3\text{C}=\text{C}$ ), 1.48 (3H, d,  $J$  = 1.2 Hz,  $\text{CH}_3\text{C}=\text{C}$ ), 1.43 (3H, dd,  $J$  = 6.6, 0.9 Hz,  $\text{CH}_3\text{CH}=\text{C}$ ), 1.07

(1H, m, CH<sub>2</sub>CH<sub>3</sub>), 0.86 (9H, s, (CH<sub>3</sub>)<sub>3</sub>C), 0.78 (3H, t, *J* = 7.4 Hz, CH<sub>3</sub>CH<sub>2</sub>), 0.68 (3H, d, *J* = 6.9 Hz, CH<sub>3</sub>CHCHOPMB), 0.02 (3H, s, CH<sub>3</sub>Si), -0.06 (3H, s, CH<sub>3</sub>Si); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 159.0, 139.2, 138.2, 133.4, 133.2, 132.9, 130.6, 129.6 (Ar C), 129.1 (Ar C), 128.1 (Ar C), 121.3 (C-40), 113.7 (Ar C), 89.8 (C-34), 82.4 (C-38), 68.9 (OCH<sub>2</sub>Ar), 55.2 (ArOCH<sub>3</sub>), 54.3 (C-31), 44.3 (C-37), 33.8 (C-33), 26.8 (C-32), 25.9 ((CH<sub>3</sub>)<sub>3</sub>C), 24.9 (C-46), 18.2 ((CH<sub>3</sub>)<sub>3</sub>CSi), 16.3 (C-44), 13.0 (C-41), 11.5 (C-47), 10.9 (C-45/48), 10.7 (C-48/45), -4.6 (SiCH<sub>3</sub>), -5.1 (SiCH<sub>3</sub>); HRMS (FAB+) Calcd. for C<sub>36</sub>H<sub>56</sub>O<sub>5</sub>SSiNa (M+Na)<sup>+</sup>: 651.35152. Found: 651.35204.

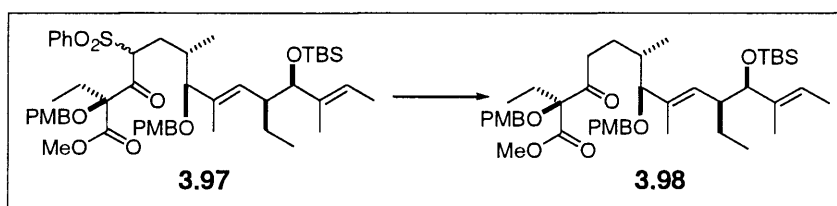
### β-Hydroxysulfone **3.96**



To a solution of phenylsulfone **3.95** (5.05 g, 8.03 mmol, azeotroped from benzene) in anhydrous THF (40 mL) at -78 °C under N<sub>2</sub> was added dropwise *n*-BuLi (2.5 M in hexanes, 3.69 mL, 9.23 mmol). The resultant yellow / orange solution was stirred at -78 °C for 45 min. A solution of aldehyde **3.5** (2.35 g, 8.83 mmol) in anhydrous THF (40 mL) was then added via syringe over 15 min. The reaction mixture was stirred at -78 °C for a further 20 min, then warmed to rt over 30 min. The reaction mixture was quenched by the addition of brine (50 mL), and the product was extracted with Et<sub>2</sub>O (3 x 40 mL). The combined organics were dried (MgSO<sub>4</sub>), filtered and concentrated under reduced pressure. Purification by SiO<sub>2</sub> flash chromatography (gradient elution 5:1 to 1:1 petrol/EtOAc) gave 6.10 g (85%) of hydroxysulfone **3.96** as a mixture of 4 diastereoisomers which was used directly in the next step.

**$\beta$ -Ketosulfone 3.97**

To a stirred solution of DMSO (2.90 mL, 40.9 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (60 mL) at  $-78^\circ\text{C}$  under  $\text{N}_2$  was added TFAA (2.88 mL, 20.4 mmol) dropwise over 5 min. The resulting mixture was stirred at  $-78^\circ\text{C}$  for 30 min, before a solution of hydroxysulfone **3.96** (6.10 g, 6.81 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (40 mL) was added via cannula over 15 min. After stirring for a further 5 min at  $-78^\circ\text{C}$ ,  $\text{Et}_3\text{N}$  (19.0 mL, 136.2 mmol) was added over 10 min, and the reaction mixture was allowed to warm to rt over 30 min. The reaction mixture was then quenched with brine (80 mL) and diluted with  $\text{CH}_2\text{Cl}_2$  (100 mL). The organic layer was separated, and the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 100 mL). The combined organics were concentrated *in vacuo*, and the crude  $\beta$ -ketosulfone **3.97** was used in the next step without further purification.

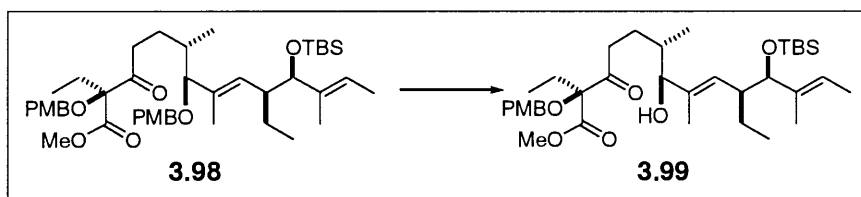
**Ketone 3.98**

Crude ketosulfone **3.97** (<6.81 mmol) was dissolved in THF- $\text{H}_2\text{O}$  (275 mL, 10:1 v:v) and the resultant solution was heated to reflux. Activated Al-Hg was then added portionwise over 20 min, until the starting material had been consumed. The activated Al-Hg was prepared by dipping strips of aluminium foil sequentially into 2 % aqueous  $\text{HgCl}_2$ , MeOH and  $\text{Et}_2\text{O}$ . The reaction mixture was then cooled to rt and filtered through celite, the filter cake being washed thoroughly with EtOAc. The filtrate was dried over anhydrous  $\text{MgSO}_4$ , filtered and



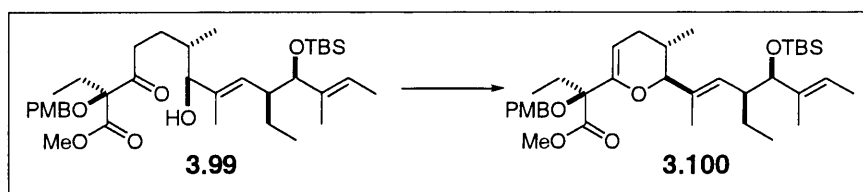
concentrated *in vacuo*. Purification by SiO<sub>2</sub> flash chromatography (8:1 petrol/EtOAc) gave 4.20 g (83 % over 2 steps) of ketone **3.98** as a clear, viscous oil. Data for **3.98**:  $[\alpha]_D^{+16.1}$  (c 1.266, CH<sub>2</sub>Cl<sub>2</sub>); IR (neat) cm<sup>-1</sup>: 2957 (s), 2932 (s), 2857 (s), 1748 (s), 1721 (m), 1613 (w), 1514 (s), 1460 (m), 1383 (w), 1301 (w), 1249 (s), 1176 (w), 1038 (s), 835 (m), 775 (w); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  7.27 (2H, m, ArH), 7.16 (2H, m, ArH), 6.85 (2H, m, ArH), 6.81 (2H, m, ArH), 5.29 (1H, q, *J* = 5.7 Hz, C=CHCH<sub>3</sub>), 4.88 (1H, d, *J* = 9.7 Hz, C=CHCH(Et)), 4.38 (1H, d, *J* = 10.7 Hz, OCH<sub>2</sub>Ar), 4.30 (1H, d, *J* = 10.7 Hz, OCH<sub>2</sub>Ar), 4.18 (1H, d, *J* = 11.1 Hz, OCH<sub>2</sub>Ar), 3.91 (1H, d, *J* = 11.1 Hz, OCH<sub>2</sub>Ar), 3.78 (3H, s, ArOCH<sub>3</sub>), 3.76 (3H, s, ArOCH<sub>3</sub>), 3.73 (1H, d, *J* = 9.0 Hz, CHOTBS), 3.67 (3H, s, CO<sub>2</sub>CH<sub>3</sub>), 3.13 (1H, d, *J* = 9.6 Hz, CHOPMB), 2.64 (2H, m, CH<sub>2</sub>C=O), 2.44 (1H, app qd, *J* = 10.0, 3.0 Hz, CH(Et)CHOTBS), 2.19 (1H, m, CH<sub>3</sub>CHHCC=O), 2.06 (1H, m, CH<sub>3</sub>CHHCC=O), 1.99 (1H, m, CHHCH<sub>2</sub>C=O), 1.84 (1H, m, CH<sub>3</sub>CHHCC=C), 1.61 (1H, m, CH(CH<sub>3</sub>)CHOPMB), 1.52 (6H, s, 2 x CH<sub>3</sub>C=C), 1.43 (3H, d, *J* = 6.7 Hz, CH<sub>3</sub>CH=C), 1.30 (1H, m, CHHCH<sub>2</sub>C=O), 1.10 (1H, m, CH<sub>3</sub>CHHCC=C), 0.86 (9H, s, (CH<sub>3</sub>)<sub>3</sub>C), 0.81 (6H, 2 x t, *J* = 7.4 Hz, 2 x CH<sub>3</sub>CH<sub>2</sub>), 0.65 (3H, d, *J* = 6.8 Hz, CH<sub>3</sub>CHCHOPMB), 0.02 (3H, s, CH<sub>3</sub>Si), -0.06 (3H, s, CH<sub>3</sub>Si); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  208.2 (C-30), 169.9 (C-28), 159.2, 158.9, 138.2, 133.8, 132.3 (C-36), 131.2, 129.8, 129.5 (Ar C), 128.9 (Ar C), 121.2 (C-40), 113.7 (Ar C), 113.6 (Ar C), 90.6 (C-34), 89.8, 82.5 (C-38), 69.0 (OCH<sub>2</sub>Ar), 66.5 (OCH<sub>2</sub>Ar), 55.3 (ArOCH<sub>3</sub>), 55.2 (ArOCH<sub>3</sub>), 52.4 (CO<sub>2</sub>CH<sub>3</sub>), 44.3 (C-37), 36.5 (C-36), 34.4, 26.9 (C-32/42), 25.9 ((CH<sub>3</sub>)<sub>3</sub>C), 24.9 (C-46), 24.5 (C-42/32), 18.2 ((CH<sub>3</sub>)<sub>3</sub>CSi), 16.1, 13.1, 11.6, 11.1, 10.8, 7.3, -4.6 (SiCH<sub>3</sub>), -5.1 (SiCH<sub>3</sub>); HRMS (FAB+) Calcd. for C<sub>44</sub>H<sub>68</sub>O<sub>8</sub>SiNa (M+Na)<sup>+</sup>: 775.45809. Found: 775.45985.

### Hydroxyketone **3.99**



To a solution of ketone **3.98** (4.05 g, 5.38 mmol) in  $\text{CH}_2\text{Cl}_2$  (80 mL) and  $\text{H}_2\text{O}$  (5 mL) was added DDQ (1.34 g, 5.92 g mmol) in one portion at  $0^\circ\text{C}$ . The resulting dark red solution was stirred at  $0^\circ\text{C}$  for 2 h. Saturated  $\text{NaHCO}_3$  solution (40 mL) was then added and the product was extracted with  $\text{CH}_2\text{Cl}_2$  (4 x 50 mL). The combined organics were washed with saturated  $\text{NaHCO}_3$  solution (2 x 50 mL), dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo*. The crude product was used in the next step without further purification as a mixture of  $\alpha$ - and  $\beta$ -hemiketals and hydroxyketone **3.99** (which was the major component of the equilibrium mixture).

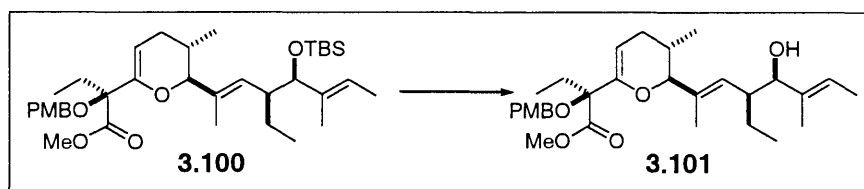
### Glycal **3.100**



To a solution of crude **3.99** (< 2.538 mmol) in anhydrous MeOH (100 mL) was added PPTS (0.27 g, 1.08 mmol) in one portion. The reaction mixture was heated at reflux at  $60^\circ\text{C}$  for 1.5 h. The reaction mixture was then cooled to rt, and saturated  $\text{NaHCO}_3$  solution (50 mL) was added. The product was extracted with EtOAc (3 x 100 mL) and then dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo*. The residue was purified by  $\text{SiO}_2$  flash chromatography (gradient elution 30:1 to 20:1 petrol/EtOAc) to give 3.02 g (91% over 2 steps) of glycal **3.100** as a clear oil. Data for **3.100**:  $[\alpha]_{\text{D}}^{20} +89.0^\circ$  (c 0.802,  $\text{CH}_2\text{Cl}_2$ ); IR (neat)  $\text{cm}^{-1}$ : 2956 (s), 2930 (s), 2857 (m), 1743 (m), 1613 (w), 1514 (m), 1460 (w), 1250 (s), 1057 (s), 836 (m), 775 (m);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.28 (2H, m, ArH), 6.83 (2H, m, ArH), 5.25 (1H, q,  $J = 6.5$  Hz,  $\text{C}=\text{CHCH}_3$ ), 4.98-4.94 (2H, m,  $\text{C}=\text{CHCH}(\text{Et})$ ),  $\text{CHC}=\text{C}(\text{O})$ ), 4.50 (1H, d,  $J = 10.8$  Hz,  $\text{OCHHAr}$ ), 4.27 (1H, d,  $J = 10.8$  Hz,  $\text{OCHHAr}$ ), 3.77 (3H, s,  $\text{ArOCH}_3$ ), 3.71 (1H, d,  $J = 7.4$  Hz), 3.70 (3H, s,  $\text{CO}_2\text{CH}_3$ ), 3.63 (1H, d,  $J = 9.5$  Hz,  $\text{CH}(\text{O})\text{CHCH}_3$ ), 2.34 (1H, m,  $\text{CH}(\text{Et})\text{CHOTBS}$ ), 2.10 (1H, m,  $\text{CHHC}=\text{C}(\text{O})$ ), 1.98 (2H, m,  $\text{CH}_3\text{CH}_2\text{CCO}_2\text{CH}_3$ ), 1.84-1.71 (3H, m,  $\text{CHHC}=\text{C}(\text{O})$ ,  $\text{CH}(\text{CH}_3)\text{CH}_2\text{C}=\text{C}$ ,  $\text{CH}_3\text{CHHCCOH}$ ), 1.53-1.49 (9H, superimposed 2 x s and 1 x d, 2 x

$\text{CH}_3\text{C}=\text{C}$ , 1 x  $\text{CH}_3\text{CH}=\text{C}$ ), 1.08 (1H, m,  $\text{CH}_3\text{CHCHCOH}$ ), 0.86 (9H, s,  $(\text{CH}_3)_3\text{C}$ ), 0.84 (3H, t,  $J = 7.4$  Hz,  $\text{CH}_3\text{CH}_2$ ), 0.79-0.76 (6H, m,  $\text{CH}_3\text{CH}_2$ ,  $\text{CH}_3\text{CH}$ ), 0.00 (3H, s,  $\text{CH}_3\text{Si}$ ), -0.07 (3H, s,  $\text{CH}_3\text{Si}$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  172.2, 158.9, 150.7, 137.2, 133.5, 131.9, 130.9, 129.0, 120.6, 113.5, 97.7, 88.1, 83.9, 81.6, 66.1, 55.2, 51.9, 44.2, 29.2, 28.6, 25.9, 25.4, 23.9, 18.2, 17.5, 12.7, 11.7, 11.6, 11.6, 7.6, -4.7, -5.1; HRMS (FAB+) Calcd. for  $\text{C}_{36}\text{H}_{58}\text{O}_6\text{SiNa}$  ( $\text{M}+\text{Na}$ ) $^+$ : 637.39001. Found: 637.38846.

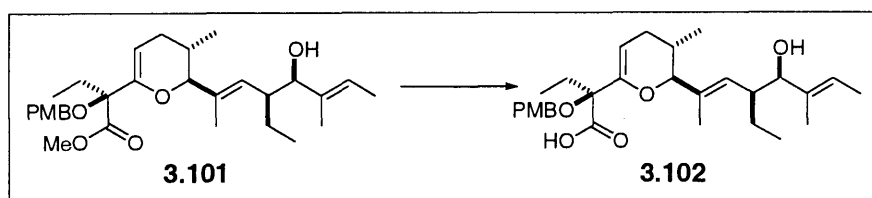
### Alcohol 3.101



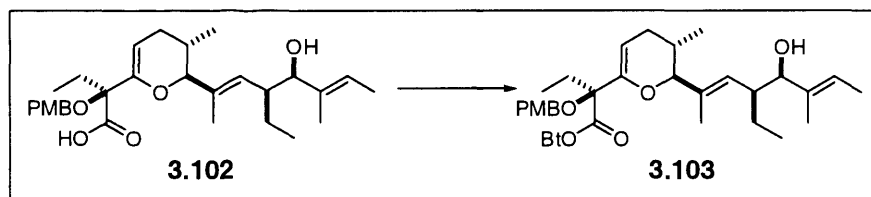
To 20 mL of 1.0 M TBAF in THF was added 20 mL of anhydrous DMF. The THF was then removed under reduced pressure on the rotary evaporator to give a 1.0 M solution of TBAF in DMF. This 1.0 M solution of TBAF in DMF was transferred via syringe to a flask containing neat glycal **3.100** (1.42 g, 2.31 mmol). The resultant mixture was stirred at RT under  $\text{N}_2$  for 12 h. The reaction mixture was then diluted with  $\text{Et}_2\text{O}$  (100 mL) and washed with  $\text{H}_2\text{O}$  (25 mL) and brine (25 mL). The organic layer was dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo*. The residue was purified by  $\text{SiO}_2$  flash chromatography (gradient elution 8:1 to 5:1 Petrol/ $\text{EtOAc}$ ) to give 735 mg (76%) of alcohol **3.101** as a clear oil. Data for **3.101**:  $[\alpha]_D^{+67.2}$  (c 0.22,  $\text{CH}_2\text{Cl}_2$ ); IR (neat)  $\text{cm}^{-1}$ : 3440 (br m), 2956 (s), 2924 (s), 2872 (m), 1741 (s), 1669 (w), 1613 (w), 1514 (s), 1455 (m), 1380 (w), 1302 (w), 1248 (s), 1131 (m), 1082 (m), 1014 (m), 824 (w);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.27 (2H, m,  $\text{ArH}$ ), 6.83 (2H, m,  $\text{ArH}$ ), 5.38 (1H, q,  $J = 6.3$  Hz,  $\text{C}=\text{CHCH}_3$ ), 5.01 (1H, d,  $J = 9.3$  Hz,  $\text{C}=\text{CHCH}(\text{Et})$ ), 4.95 (1H, dd,  $J = 5.5, 2.2$  Hz,  $\text{CHC}=\text{C}(\text{O})$ ), 4.51 (1H, d,  $J = 10.8$  Hz,  $\text{OCHHAr}$ ), 4.27 (1H, d,  $J = 10.8$  Hz,  $\text{OCHHAr}$ ), 3.81 (1H, d,  $J = 7.9$  Hz,  $\text{CHOH}$ ), 3.77 (3H, s,  $\text{ArOCH}_3$ ), 3.70 (3H, s,  $\text{CO}_2\text{CH}_3$ ), 3.63 (1H, d,  $J = 9.5$  Hz,  $\text{CH}(\text{O})\text{CHCH}_3$ ), 2.41 (1H, m,  $\text{CH}(\text{Et})\text{CHOH}$ ), 2.11 (1H, app dt,  $J = 16.3, 4.9$  Hz,  $\text{CHHC}=\text{C}(\text{O})$ ), 1.98 (2H, m,  $\text{CH}_3\text{CH}_2\text{CCO}_2\text{CH}_3$ ), 1.84-1.71 (3H, m,  $\text{CHHC}=\text{C}(\text{O})$ ),

$\text{CH}(\text{CH}_3)\text{CH}_2\text{C}=\text{C}$ ,  $\text{CH}_3\text{CHHCCOH}$ ), 1.55-1.54 (9H, superimposed 2 x s and 1 x d, 2 x  $\text{CH}_3\text{C}=\text{C}$ , 1 x  $\text{CH}_3\text{CH}=\text{C}$ ), 1.15 (1H, m,  $\text{CH}_3\text{CHHCCOH}$ ), 0.84 (3H, t,  $J = 7.4$  Hz,  $\text{CH}_3\text{CH}_2$ ), 0.82 (3H, t,  $J = 7.5$  Hz,  $\text{CH}_3\text{CH}_2$ ), 0.78 (3H, d,  $J = 6.6$  Hz,  $\text{CH}_3\text{CH}$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  172.3 (C-28), 158.9, 150.7, 137.3, 134.3, 131.04 (C-36?), 130.99 (C-36?), 129.0 (Ar C), 121.6 (C-40), 113.5 (Ar C), 98.0 (C-31), 87.9 (C-34), 84.0, 80.9 (C-38), 66.2 ( $\text{OCH}_2\text{Ar}$ ), 55.2 ( $\text{ArOCH}_3$ ), 51.9 ( $\text{CO}_2\text{CH}_3$ ), 43.5 (C-37), 29.2 (C-32), 28.6, 25.7 (C-42), 24.1 (C-46), 17.4 (C-33), 12.9, 11.68, 11.66, 11.64, 7.7; HRMS (FAB+) Calcd. for  $\text{C}_{30}\text{H}_{44}\text{O}_6\text{Na}$  ( $\text{M}+\text{Na}$ ) $^+$ : 523.30354. Found: 523.30202.

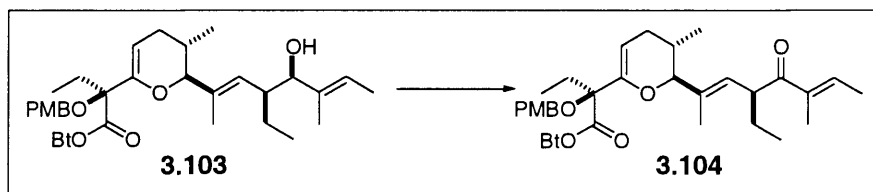
### Carboxylic acid **3.102**



To a solution of EtSH (0.70 mL, 10.1 mmol) in anhydrous THF (10 mL) at 0 °C under  $\text{N}_2$  was added  $n\text{-BuLi}$  (2.5 M in hexanes, 3.72 mL, 9.3 mmol). The resultant white, cloudy solution was stirred at 0 °C for 30 min. A solution of alcohol **3.101** (1.01 g, 1.51 mmol) in anhydrous HMPA (20 mL) was then added via cannula over 10 min. The reaction mixture was warmed to rt, and stirred at rt for 1.5 h. The reaction mixture was diluted with EtOAc (200 mL) and acidified to pH 6 with 2 M aqueous  $\text{NaHSO}_4$ . The organic layer was separated, and the aqueous phase extracted with EtOAc (100 mL). The aqueous layer was then further acidified to pH 4 with 2 M aqueous  $\text{NaHSO}_4$  and re-extracted with EtOAc (100 mL). The combined organics were washed with water (100 mL) and brine (100 mL), dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo*. The crude product, acid **3.102**, was then used in the next step without further purification.

***N*-Hydroxybenzotriazolyl ester **3.103****

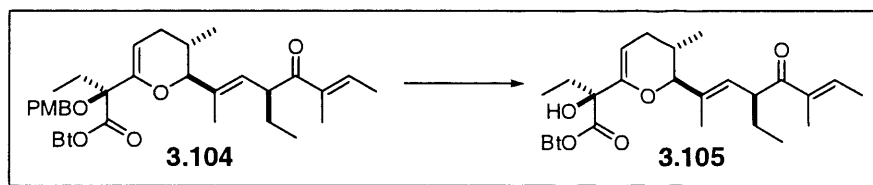
To a solution of crude carboxylic acid **3.102** (<2.02 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (25 mL) at rt under  $\text{N}_2$  was added  $i\text{-PrNEt}_2$  (1.2 mL) followed by BOP reagent (1.79 g, 4.04 mmol). The reaction mixture was stirred at rt for 25 min, then diluted with EtOAc (50 mL) and washed with  $\text{H}_2\text{O}$  (2 x 25 mL). The organic layer was then dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo*. The residue was purified by  $\text{SiO}_2$  flash chromatography (gradient elution 10:1 to 6:1 petrol/EtOAc) to give 882 mg (72% over 2 steps) of *N*-Hydroxybenzotriazolyl activated ester **3.103** as a colourless oil. Data for **3.103**:  $[\alpha]_D^{+72.0}$  (c 0.52,  $\text{CH}_2\text{Cl}_2$ ); IR (neat)  $\text{cm}^{-1}$ : 3420 (br m), 2928 (s), 2872 (m), 1817 (m), 1671 (w), 1614 (m), 1515 (s), 1444 (m), 1381 (m), 1250 (s), 1037 (s), 824 (w), 744 (m);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.04 (1H, m, ArH), 7.50 (1H, m, ArH), 7.39 (1H, m, ArH), 7.34 (3H, m, ArH), 6.86 (2H, m, ArH), 5.39 (1H, q,  $J$  = 6.6 Hz,  $\text{C}=\text{CHCH}_3$ ), 5.27 (1H, dd,  $J$  = 5.4, 2.1 Hz,  $\text{CH}_2\text{CH}=\text{C}(\text{O})$ ), 5.23 (1H, d,  $J$  = 10.3 Hz,  $\text{C}=\text{CHCH}(\text{Et})$ ), 4.67 (1H, d,  $J$  = 10.5 Hz,  $\text{OCH}_2\text{Ar}$ ), 4.53 (1H, d,  $J$  = 10.5 Hz,  $\text{OCH}_2\text{Ar}$ ), 3.87 (1H, d,  $J$  = 7.2 Hz,  $\text{CH}_2\text{OH}$ ), 3.84 (1H, d,  $J$  = 9.6 Hz,  $\text{CH}_3\text{CHCH}(\text{O})$ ), 3.78 (3H, s,  $\text{ArOCH}_3$ ), 2.45 (1H, m,  $\text{CH}(\text{Et})\text{CHOH}$ ), 2.25 (3H, m,  $\text{CH}_3\text{CH}_2\text{CCO}_2\text{Bt}$ ,  $\text{CHHC}=\text{C}(\text{O})$ ), 1.76 (1H, m,  $\text{CH}_3\text{CHHCHOH}$ ), 1.66 (3H, s,  $\text{CH}_3\text{C}=\text{C}$ ), 1.53 (3H, s,  $\text{CH}_3\text{C}=\text{C}$ ), 1.48 (3H, d,  $J$  = 6.7 Hz,  $\text{CH}_3\text{CH}=\text{C}$ ), 1.19 (1H, m,  $\text{CH}_3\text{CHHCHOH}$ ), 1.07 (3H, t,  $J$  = 7.4 Hz,  $\text{CH}_3\text{CH}_2\text{CCO}_2\text{Bt}$ ), 0.86 (3H, d,  $J$  = 6.6 Hz,  $\text{CH}_3\text{CH}$ ), 0.83 (3H, t,  $J$  = 7.5 Hz,  $\text{CH}_3\text{CH}_2\text{CCHOH}$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  168.3 (C-28), 159.2, 149.1, 143.5, 137.0, 133.6, 132.5 (C-36), 130.0, 129.3 (Ar C), 128.7, 128.6 (Ar C), 124.7 (Ar C), 121.2 (C-40), 120.5 (Ar C), 113.8 (Ar C), 108.3 (Ar C), 100.3 (C-31), 88.7 (C-34), 84.1, 80.5 (C-38), 66.9 ( $\text{OCH}_2\text{Ar}$ ), 55.3 ( $\text{ArOCH}_3$ ), 43.3 (C-37), 29.4 (C-32), 29.0, 26.1 (C-42), 23.5 (C-46), 17.4 (C-44), 12.8, 12.1, 11.9, 11.8, 7.7; HRMS (FAB+) Calcd. for  $\text{C}_{35}\text{H}_{45}\text{O}_6\text{N}_3\text{Na}$  ( $\text{M}+\text{Na}$ ) $^+$ : 626.32059. Found: 626.32155.

Ketone **3.104**

To a stirred solution of DMSO (0.57 mL, 8.00 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (15 mL) at  $-78^\circ\text{C}$  under  $\text{N}_2$  was added TFAA (0.56 mL, 4.00 mmol) dropwise over 2 min. The resultant mixture was stirred at  $-78^\circ\text{C}$  for 30 min, and then a solution of alcohol **3.103** (805 mg, 1.33 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (15 mL) was added dropwise over 10 min. The reaction mixture was stirred at  $-78^\circ\text{C}$  for 5 min, then  $\text{Et}_3\text{N}$  (3.72 mL, 26.7 mmol) was added dropwise and the mixture was allowed to warm to rt over 30 min. The reaction mixture was then diluted with  $\text{CH}_2\text{Cl}_2$  (150 mL) and washed with brine (50 mL). The organic layer was dried over anhydrous  $\text{MgSO}_4$ , filtered and concentrated *in vacuo*. Purification by  $\text{SiO}_2$  flash chromatography (gradient elution 10:1 to 5:1 petrol/ $\text{EtOAc}$ ) gave 574 mg (73%) of ketone **3.104** as a clear, viscous oil. Data for **3.104**:  $[\alpha]_{\text{D}}^{25} +113.0^\circ$  ( $c$  0.346,  $\text{CH}_2\text{Cl}_2$ ); IR (neat)  $\text{cm}^{-1}$ : 2963 (s), 2930 (s), 2874 (m), 1818 (s), 1657 (s), 1614 (m), 1514 (s), 1443 (m), 1382 (m), 1303 (w), 1250 (s), 1047 (s), 892 (w), 823 (w), 745 (m);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.01 (1H, d,  $J = 8.4$  Hz, ArH), 7.46 (1H, t,  $J = 7.3$  Hz, ArH), 7.37 (1H, t,  $J = 7.4$  Hz, ArH), 7.32 (2H, d,  $J = 8.3$  Hz, ArH), 7.26 (1H, d,  $J = 8.3$  Hz, ArH), 6.85 (1H, d,  $J = 8.7$  Hz, ArH), 6.78 (1H, q,  $J = 6.6$  Hz,  $\text{C}=\text{CHCH}_3$ ), 5.61 (1H, d,  $J = 9.7$  Hz,  $\text{C}=\text{CHCH}(\text{Et})$ ), 5.27 (1H, dd,  $J = 5.7, 1.9$  Hz,  $\text{CH}_2\text{CH}=\text{C}(\text{O})$ ), 4.66 (1H, d,  $J = 10.5$  Hz,  $\text{OCHHAr}$ ), 4.49 (1H, d,  $J = 10.5$  Hz,  $\text{OCHHAr}$ ), 4.03 (1H, dt,  $J = 13.9, 7.1$  Hz,  $\text{CH}(\text{Et})\text{C}=\text{O}$ ), 3.93 (1H, d,  $J = 9.7$  Hz,  $\text{CH}(\text{O})\text{CHCH}_3$ ), 3.77 (3H, s,  $\text{ArOCH}_3$ ), 2.24 (3H, m,  $\text{CH}_3\text{CH}_2\text{CCO}_2\text{Bt}$ ,  $\text{CHHC}=\text{C}(\text{O})$ ), 1.97-1.87 (2H, m,  $\text{CHHC}=\text{C}(\text{O})$ ,  $\text{CHCH}_3$ ), 1.81 (3H, dd,  $J = 6.9, 0.9$  Hz,  $\text{CH}_3\text{CH}=\text{C}$ ), 1.77 (3H, s,  $\text{CH}_3\text{C}=\text{C}$ ), 1.74 (1H, m,  $\text{CH}_3\text{CHHCC}=\text{O}$ ), 1.72 (3H, d,  $J = 1.2$  Hz,  $\text{CH}_3\text{C}=\text{C}$ ), 1.49 (1H, m,  $\text{CH}_3\text{CHHCC}=\text{O}$ ), 1.09 (3H, t,  $J = 7.4$  Hz,  $\text{CH}_3\text{CH}_2\text{CCO}_2\text{Bt}$ ), 0.87 (3H, d,  $J = 6.4$  Hz,  $\text{CH}_3\text{CH}$ ), 0.85 (3H, t,  $J = 7.4$  Hz,  $\text{CH}_3\text{CH}_2\text{CC}=\text{O}$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  202.8 (C-38), 168.2 (C-28), 159.2, 149.0, 143.4, 138.3, 137.5 (C-40), 134.1 (C-36), 130.5, 130.0, 129.2, 128.9, 128.6, 124.7 (Ar C), 120.2 (Ar C), 113.7 (Ar C), 108.3 (Ar C), 100.6 (C-

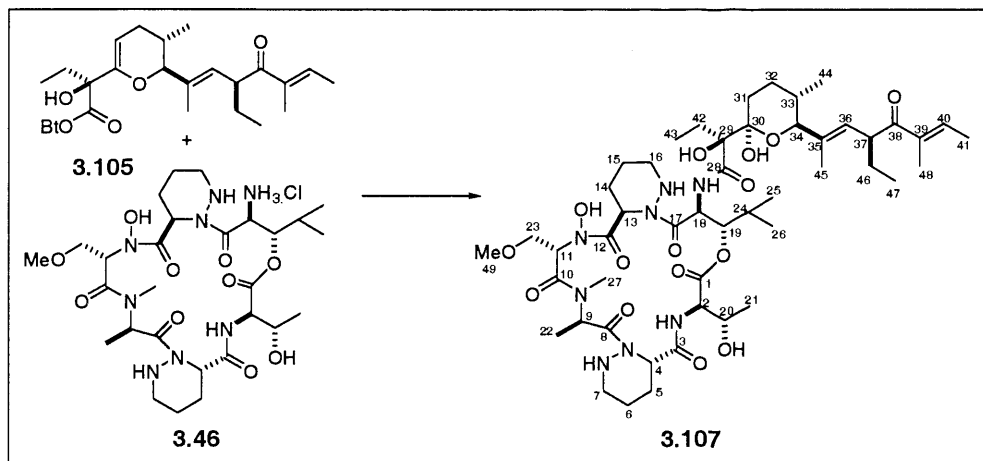
31), 88.3 (C-34), 84.0, 66.7 ( $\text{OCH}_2\text{Ar}$ ), 55.2 ( $\text{ArOCH}_3$ ), 46.0 (C-37), 29.3, 28.8, 26.9, 26.3, 17.4 (C-44), 14.9 (C-41), 11.9, 11.6, 11.3, 7.7 (C-43); HRMS (FAB+) Calcd. for  $\text{C}_{35}\text{H}_{43}\text{O}_6\text{N}_3\text{Na}$  ( $\text{M}+\text{Na}$ )<sup>+</sup>: 625.31276. Found: 625.31158.

### Alcohol **3.105**



To a stirred solution of ketone **3.104** (210 mg, 0.35 mmol) in 10 mL of wet  $\text{CDCl}_3$  was added DDQ (199 mg, 0.88 mmol) at rt. The reaction mixture was stirred vigorously at rt for 3 h before being diluted with  $\text{Et}_2\text{O}$  (80 mL) and washed with saturated  $\text{NaHCO}_3$  solution (3 x 25 mL). A further wash with brine (25 mL) was carried out before the organic layer was dried over anhydrous  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient elution 8:1 to 6:1 petrol/ $\text{EtOAc}$ ) to give a colourless oil. A second chromatographic purification ( $\text{SiO}_2$ , 6:1 petrol/ $\text{EtOAc}$ ) was then performed to rigorously ensure complete removal of any residual DDQ. This gave 121 mg (72%) of **3.105** as a colourless oil.

### Azinothricin **3.107**

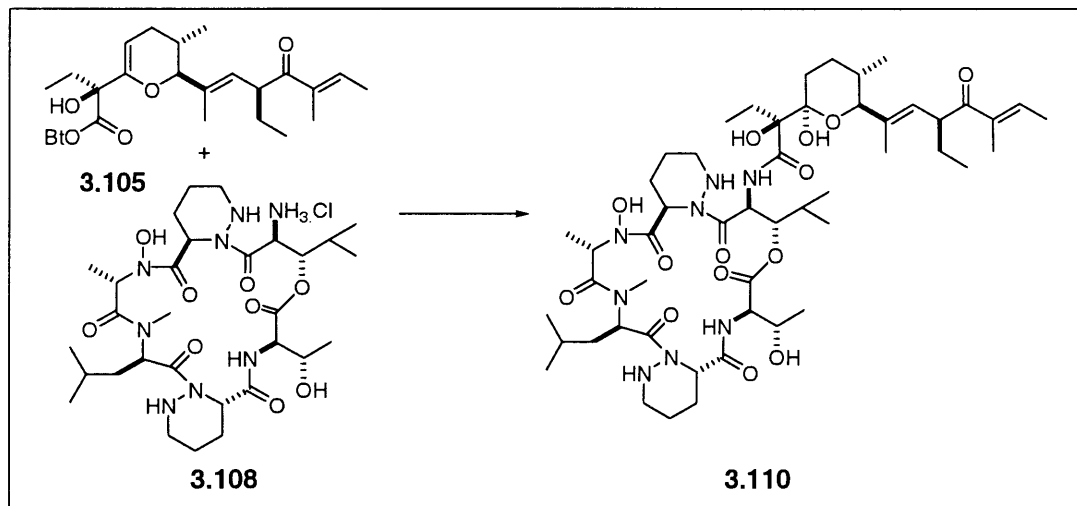


A solution of activated ester **3.105** (125 mg, 0.259 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (1 mL) was added dropwise to a flask containing the azinotricin cyclodepsipeptide salt **3.46** (180 mg, 0.259 mmol) at  $-78\text{ }^\circ\text{C}$ . The reactants were stirred at  $-78\text{ }^\circ\text{C}$  for 2 min before dropwise addition of  $\text{Et}_3\text{N}$  (0.07 mL, 0.52 mmol). The reaction mixture was stirred at  $-78\text{ }^\circ\text{C}$  for 10 min, then allowed to warm to rt over 20 min and stirred at rt for a further 10 min. The mixture was then diluted with EtOAc (100 mL) and washed with 0.5 M aq. HCl saturated with NaCl (2 x 50 mL) followed by brine (50 mL). The organic layer was then dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The crude residue was then subjected to flash chromatography on silica gel (10:1  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  as eluent) followed by preparative TLC (15:1  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  as eluent). Finally, another purification by flash chromatography on silica gel (gradient elution, 5:1 petrol/EtOAc to neat EtOAc) gave 14 mg (6%) of azinotricin **3.107** as a white amorphous solid, as determined by  $^1\text{H}$  and  $^{13}\text{C}$  NMR. Data for **3.107**:  $[\alpha]_{\text{D}} +70.7\text{ }^\circ$  (*c* 0.28,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.96 (1H, s, NOH), 8.20 (1H, d,  $J = 10.8\text{ Hz}$ , NH), 6.71 (1H, q,  $J = 7.0\text{ Hz}$ , 40-CH), 6.24 (1H, s, OH), 6.20 (1H, d,  $J = 8.5\text{ Hz}$ , NH), 6.10 (1H, q,  $J = 7.0\text{ Hz}$ , 9-CH), 5.53 (1H, d,  $J = 8.6\text{ Hz}$ , 36-CH), 5.39 (1H, dd,  $J = 10.7, 2.2\text{ Hz}$ , 19-CH), 5.32 (1H, t,  $J = 7.0\text{ Hz}$ , 11-CH), 5.18 (1H, m, 4-CH), 4.89 (2H, m, 13-CH, 18-CH), 4.77 (1H, q,  $J = 6.4\text{ Hz}$ , 20-CH), 4.51 (1H, d,  $J = 8.5\text{ Hz}$ , 2-CH), 4.40 (1H, d,  $J = 13.4\text{ Hz}$ , NH), 4.33 (1H, s, OH), 3.97 (1H, d,  $J = 10.2\text{ Hz}$ , 34-CH), 3.93 (1H, dt,  $J = 9.4, 6.8\text{ Hz}$ , 37-CH), 3.84 (2H, m, 23-CH, NH), 3.74 (1H, m, 23-CH), 3.34 (3H, s, 49-Me), 3.28 (1H, m, 7-CH), 3.12 (1H, m, 16-CH), 3.03 (3H, s, 27-Me), 2.98 (1H, m, 16-CH), 2.91 (1H, s, OH), 2.55 (2H, m, 5-CH, 7-CH), 2.23 (1H, d,  $J = 14.4\text{ Hz}$ , 14-CH), 2.01 (1H, m, 42-CH), 1.84 (3H, d,  $J = 6.1\text{ Hz}$ , 41-Me), 1.75 (3H, s, 48-Me), 1.75-1.37 (11H, overlapped m, 42-CH, 46-CH<sub>2</sub>, 6-CH<sub>2</sub>, 15-CH<sub>2</sub>, 24-CH, 31-CH, 32-CH, 33-CH, 14-CH), 1.56 (3H, d,  $J = 1.1\text{ Hz}$ , 45-Me), 1.24 (3H, d,  $J = 6.7\text{ Hz}$ , 22-Me), 1.04 (3H, d,  $J = 6.5\text{ Hz}$ , 21-Me), 0.86-0.77 (9H, m, 26-Me, 43-Me, 47-Me), 0.71 (3H, d,  $J = 6.5\text{ Hz}$ , 25-Me), 0.68 (3H, d,  $J = 6.9\text{ Hz}$ , 44-Me);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  202.7 (C-38), 175.3 (C-28), 173.2 (C-8), 172.9 (C-12), 171.1 (C-10), 170.9 (C-17), 170.4 (C-1), 169.6 (C-3), 138.5 (C-39), 136.8 (C-40), 133.8 (C-35), 128.5 (C-36), 99.6 (C-30), 82.6 (C-34), 80.1 (C-29), 78.7 (C-19), 68.6 (C-23), 64.8 (C-20), 59.2 (C-49), 56.3 (C-2), 54.7 (C-18), 53.9 (C-11), 52.5 (C-4), 51.3 (C-13), 48.0 (C-7), 47.7 (C-9), 45.7 (C-16), 45.3 (C-37), 32.4 (C-33), 29.7 (C-24), 29.4 (C-27), 28.3 (C-31), 27.8 (C-47), 27.3 (C-32), 26.0 (C-42), 24.5 (C-5),



24.1 (C-14), 21.4 (C-6), 21.2 (C-15), 19.3 (C-25), 18.9 (C-21), 17.8 (C-44), 14.9 (C-41), 14.8 (C-26), 13.2 (C-22), 12.2 (C-45), 11.9 (C-47), 11.4 (C-48), 8.3 (C-43); HRMS (FAB+) Calcd. for  $C_{49}H_{80}N_8O_{15}$  ( $M+Na$ )<sup>+</sup>: 1043.56406. Found: 1043.56043.

### Azinothricin-GE3 hybrid **3.110**



To activated ester **3.105** (70 mg, 0.145 mmol) in a round-bottomed flask was added the azinothricin cyclodepsipeptide salt **3.108** (103 mg, 0.145 mmol). The reaction flask was then purged with  $N_2$  and cooled to  $-78\text{ }^{\circ}\text{C}$ , and DMF (1 mL) and  $Et_3N$  (0.04 mL, 0.290 mmol) were added. The reaction mixture was stirred at  $-78\text{ }^{\circ}\text{C}$  for 10 min, then gradually warmed to rt over 30 min and stirred at rt for a further 10 min. The reaction mixture was then diluted with EtOAc (25 mL) and washed sequentially with 0.5 M aq. HCl (10 mL), sat. aq.  $NaHCO_3$  solution (10 mL) and brine (10 mL). The organic layer was then dried over  $MgSO_4$  and concentrated under reduced pressure. The crude residue was then purified by preparative TLC using 1:1 petrol/EtOAc as the eluent. The material was then dissolved in wet  $CDCl_3$  and stored at rt for 3 days to effect the chemoselective hydration of the glycal unit to give 42 mg (28%) of azinothricin-GE3 hybrid **3.110** as an amorphous white solid. Data for **3.110**:  $^{13}\text{C}$  NMR (125 MHz,  $CDCl_3$ ):  $\delta$  202.70, 175.26, 174.12, 173.63, 172.24, 171.07, 170.91, 170.26, 169.54, 138.50, 136.77, 133.79, 128.49, 99.62, 82.53, 80.14, 78.56, 68.92, 68.80, 64.81, 57.82, 56.29, 54.73, 52.24, 51.72, 50.81, 49.47, 47.77, 45.67, 45.26, 36.54, 32.43, 29.45, 29.33, 28.34, 27.78, 27.32, 26.03, 24.88, 24.43, 22.79, 22.71, 21.48, 21.24, 19.30, 18.97, 17.74,

14.92, 14.74, 13.37, 12.25, 11.92, 11.37, 8.22; HRMS (FAB+) Calcd. for  $C_{51}H_{84}N_8O_{14}$

(M+Na)<sup>+</sup>: 1055.60044, Found: 1055.59560.

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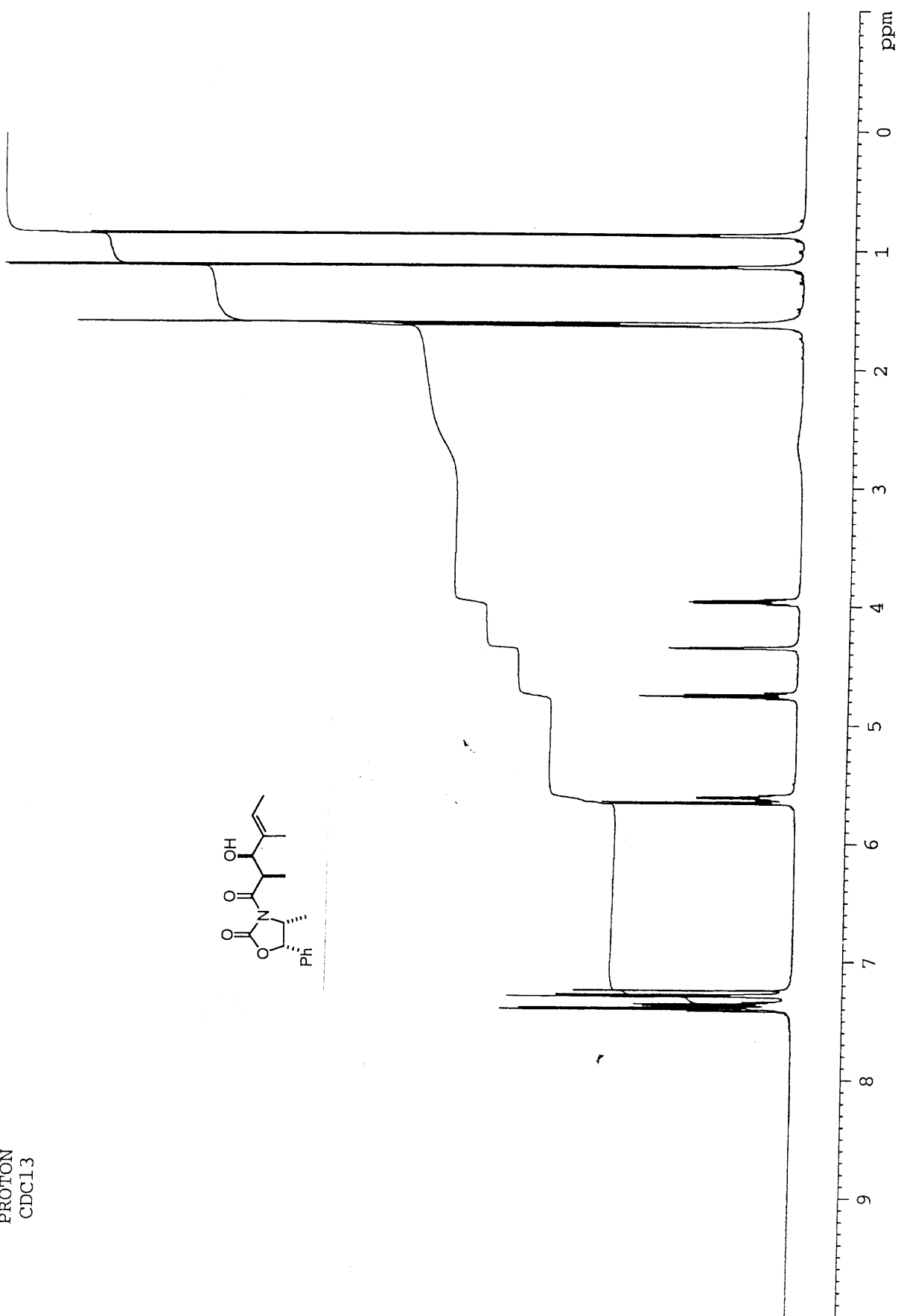
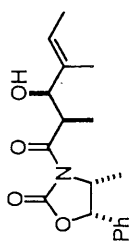
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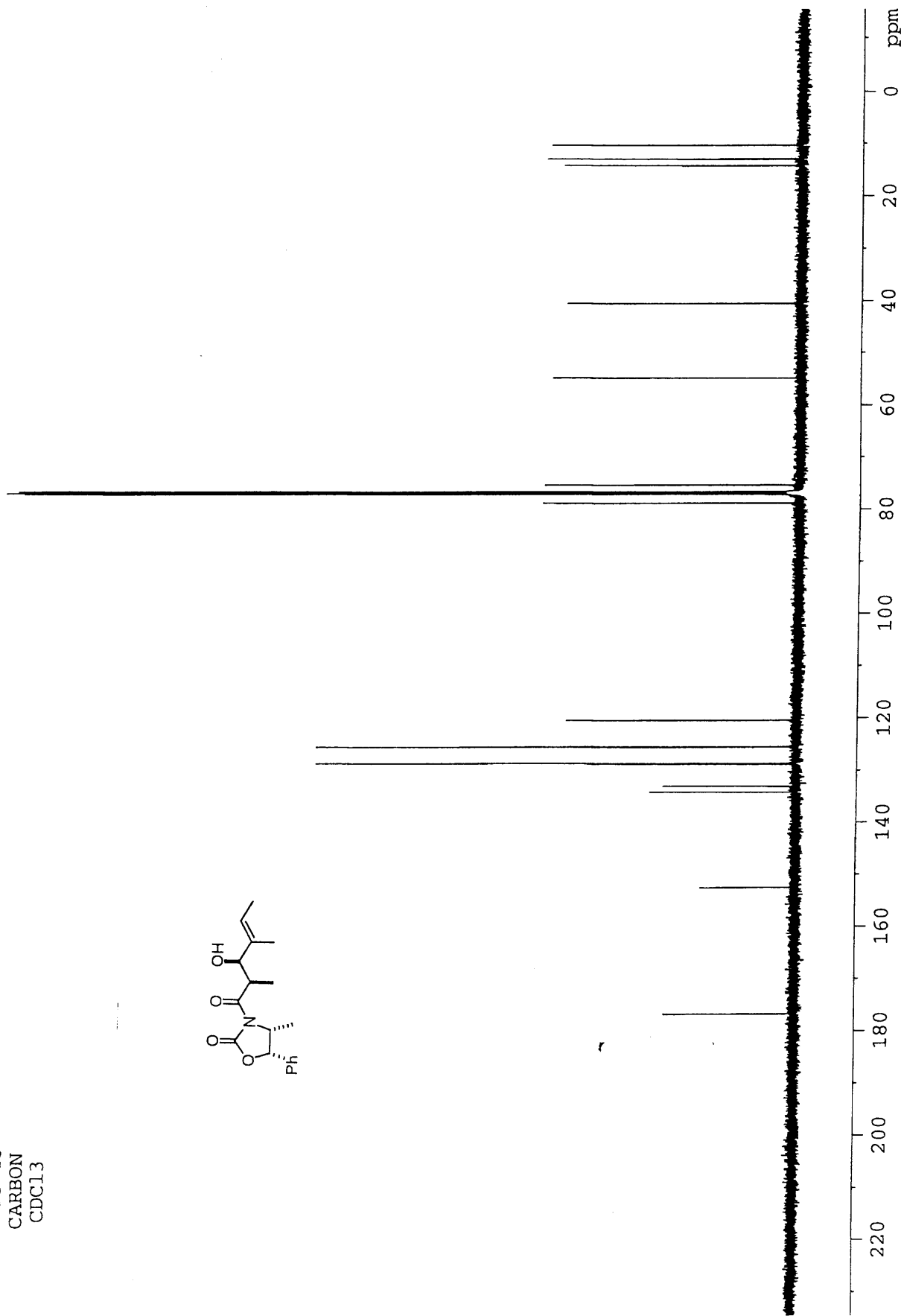
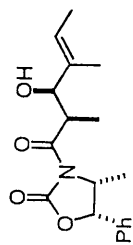
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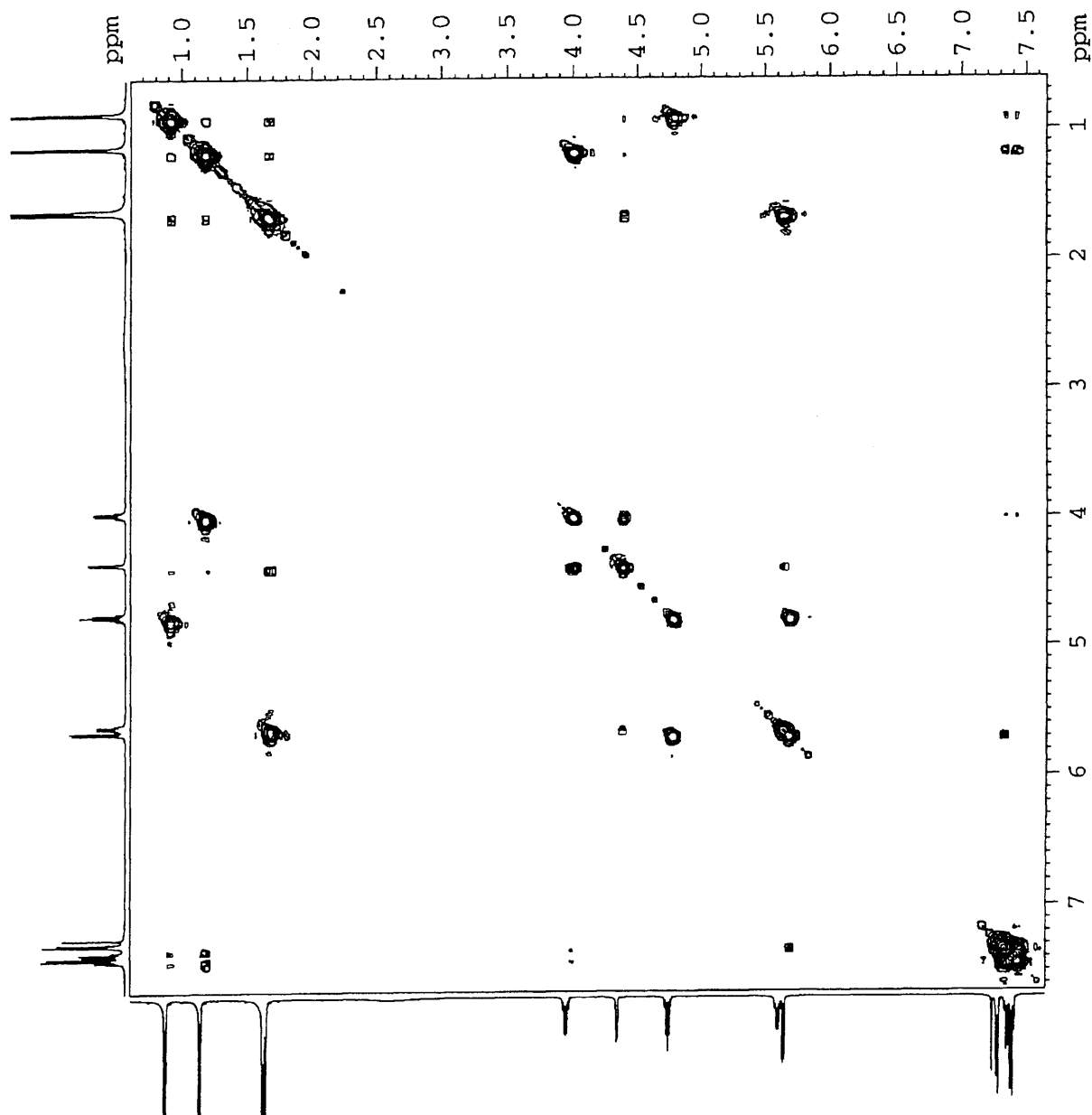
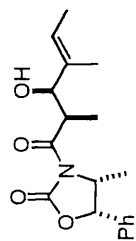
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PROTON  
CDCl3



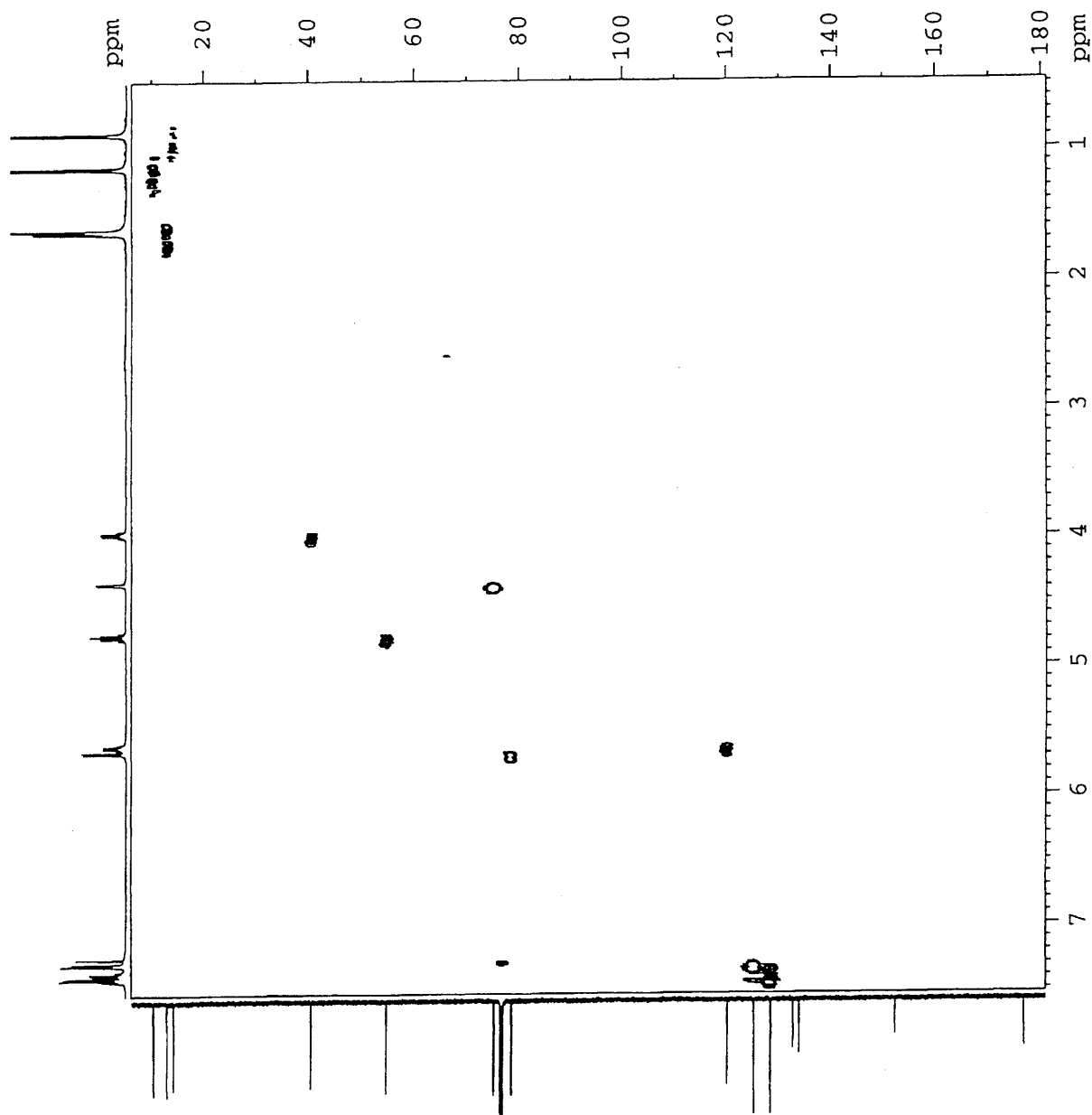
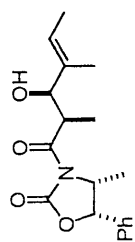
I-JG-43  
CARBON  
CDCl<sub>3</sub>



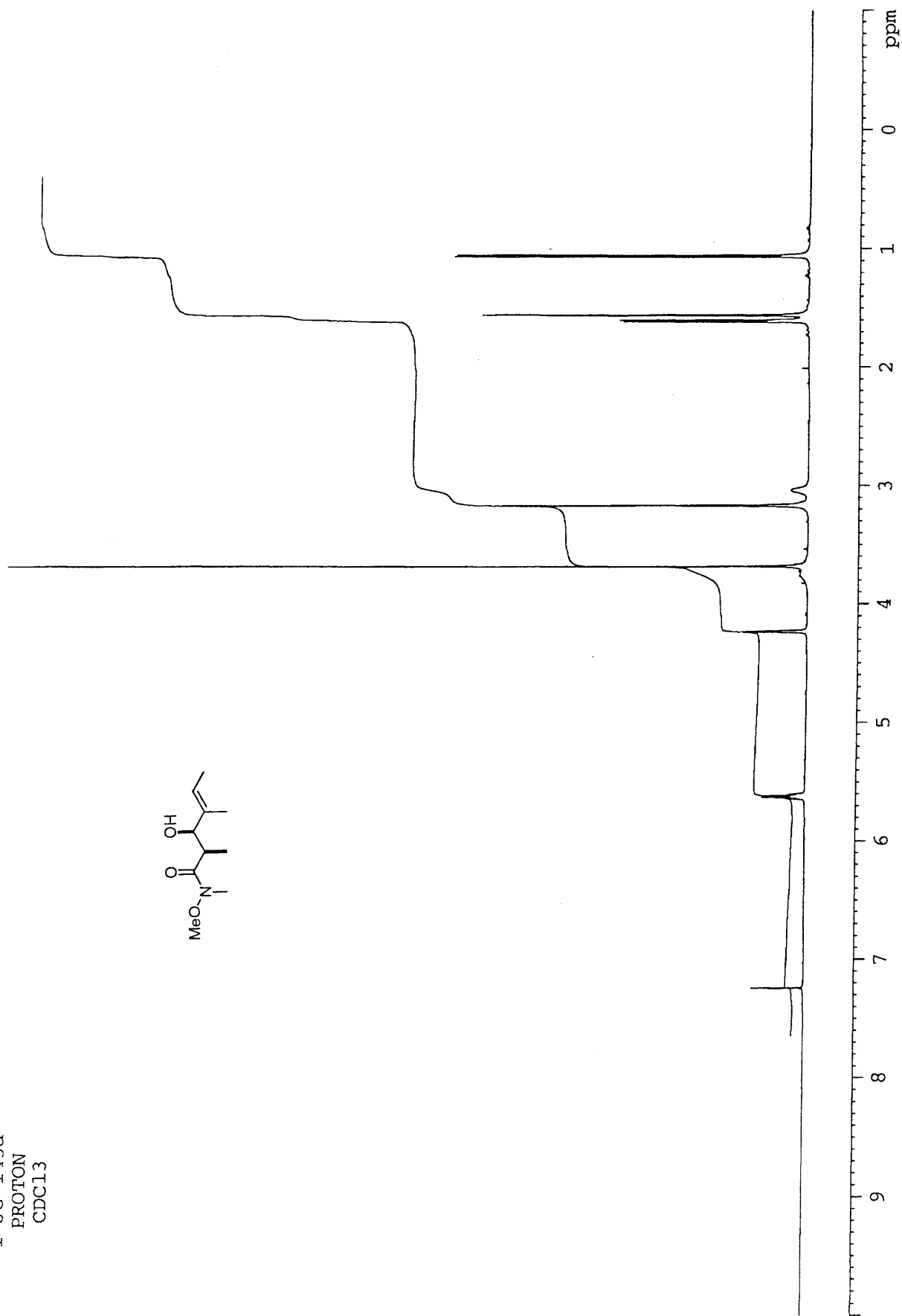
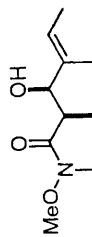
I-JG-43  
COSY  
CDCl<sub>3</sub>



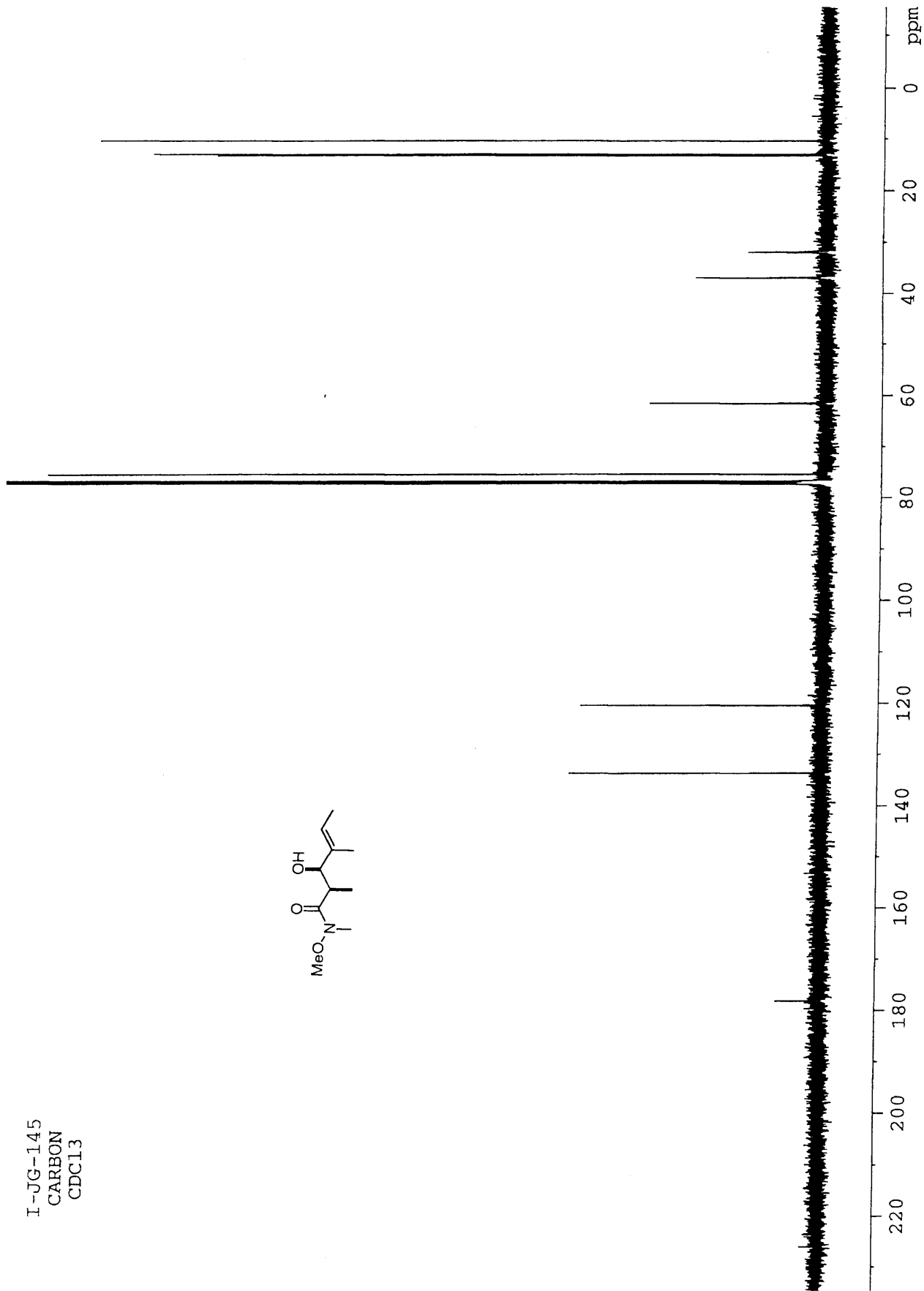
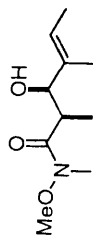
I-JG-43  
HMQC  
CDCl<sub>3</sub>



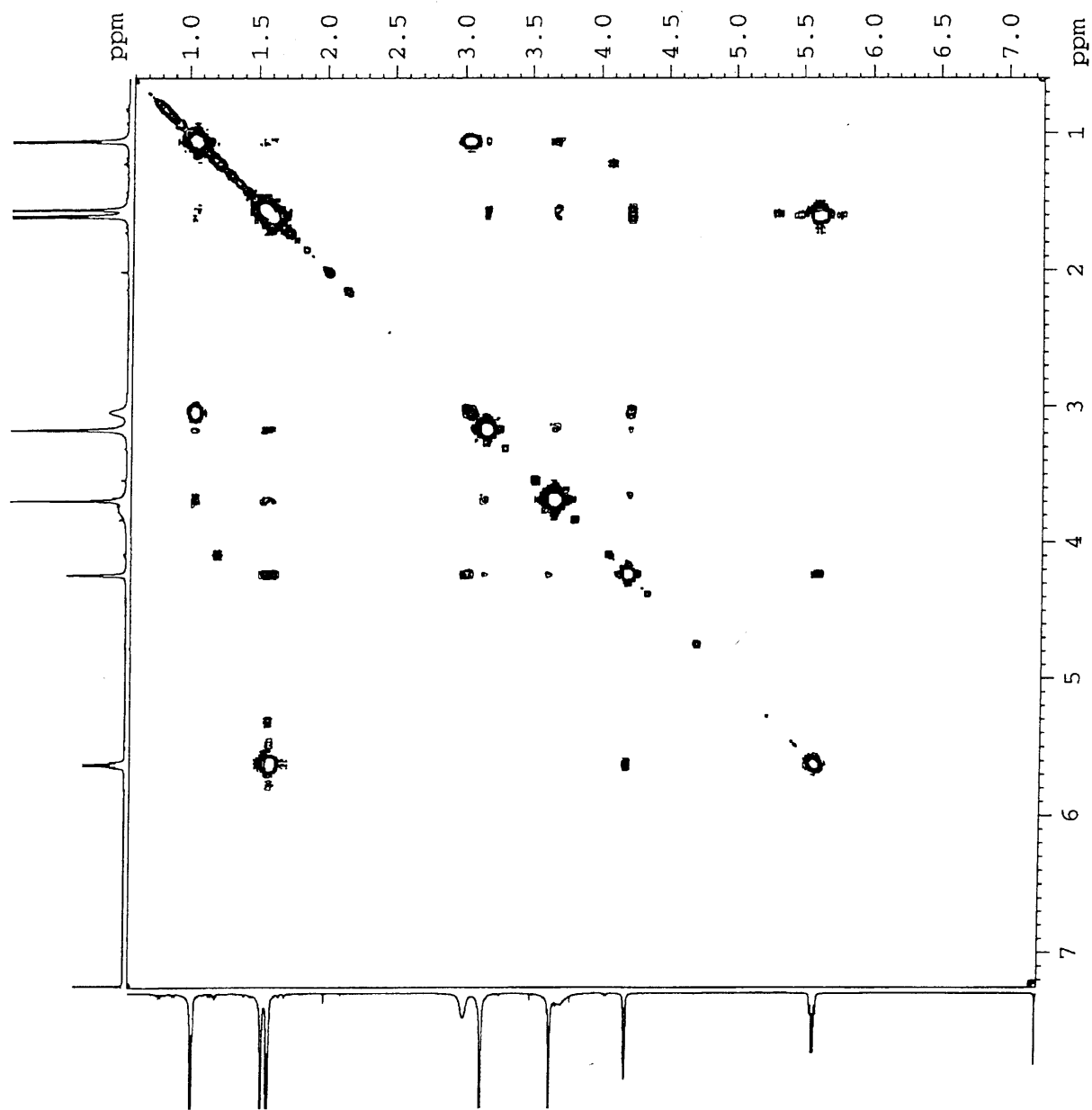
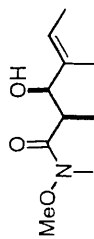
I-JG-145a  
PROTON  
CDCl3



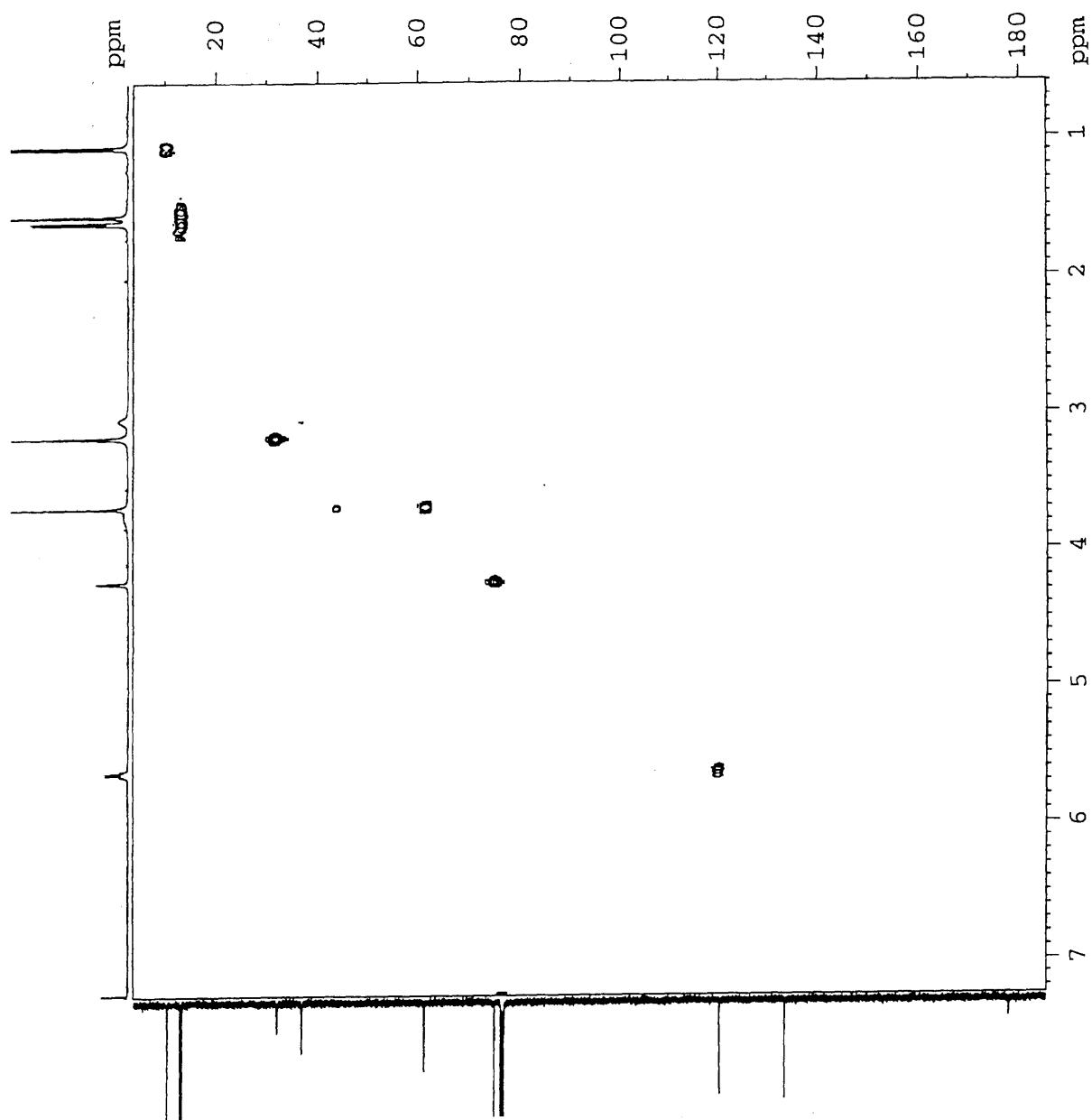
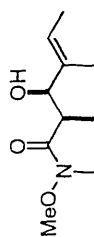
I-JG-145  
CARBON  
CDCl<sub>3</sub>



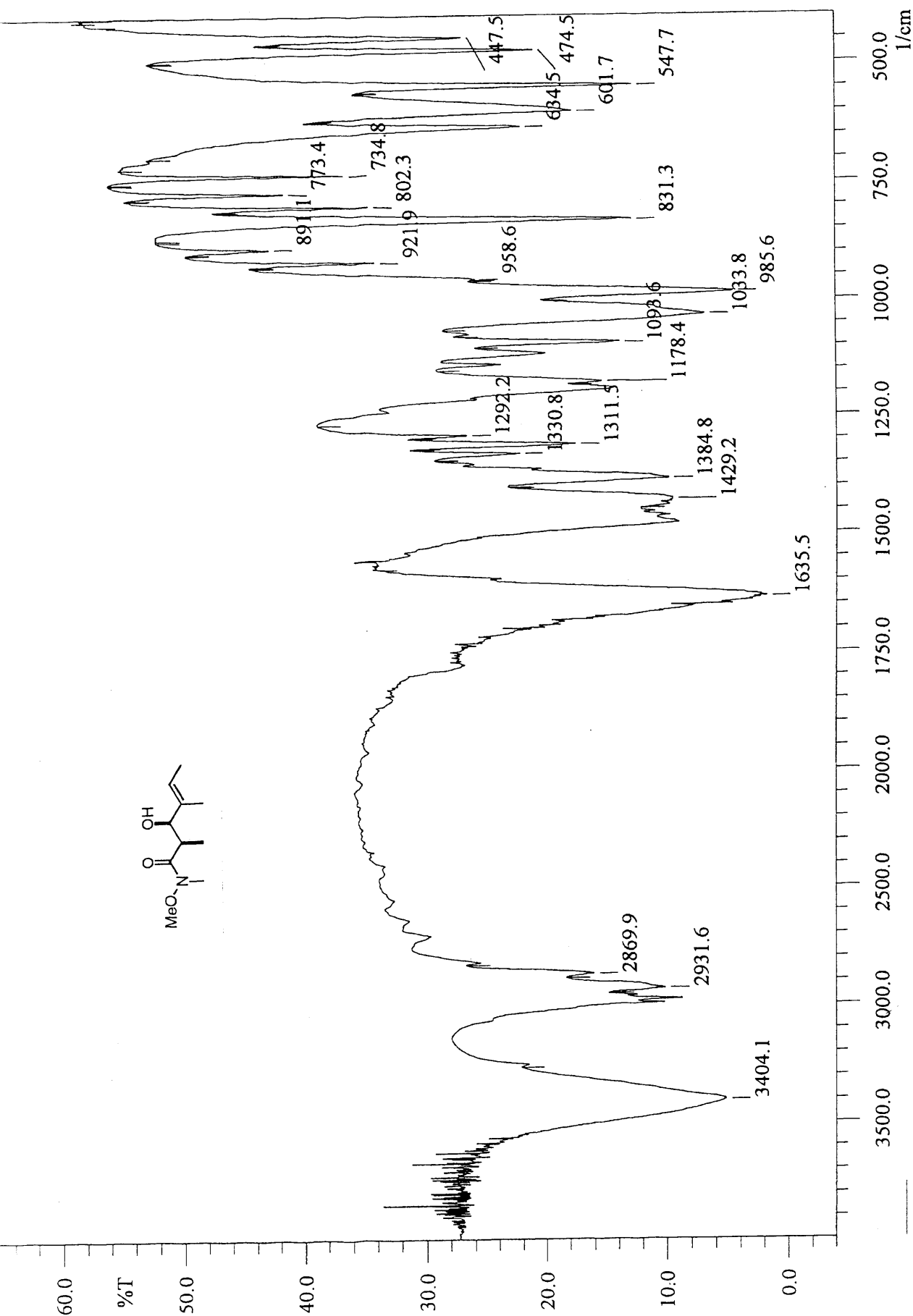
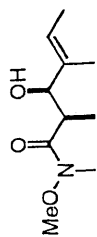
I-JG-145  
COSY  
CDCl3



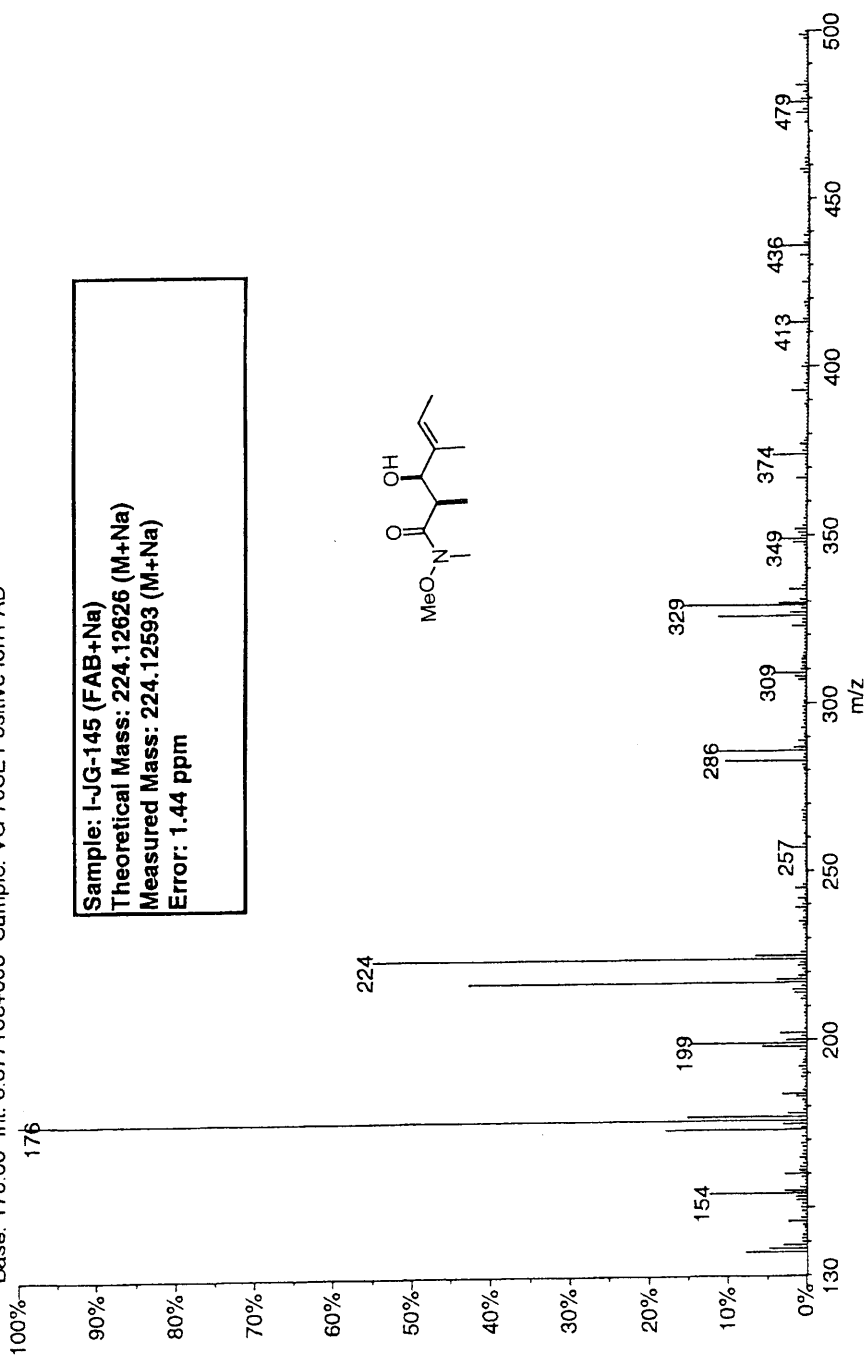
I-JG-145  
HMQC  
CDCl<sub>3</sub>



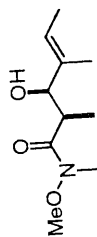


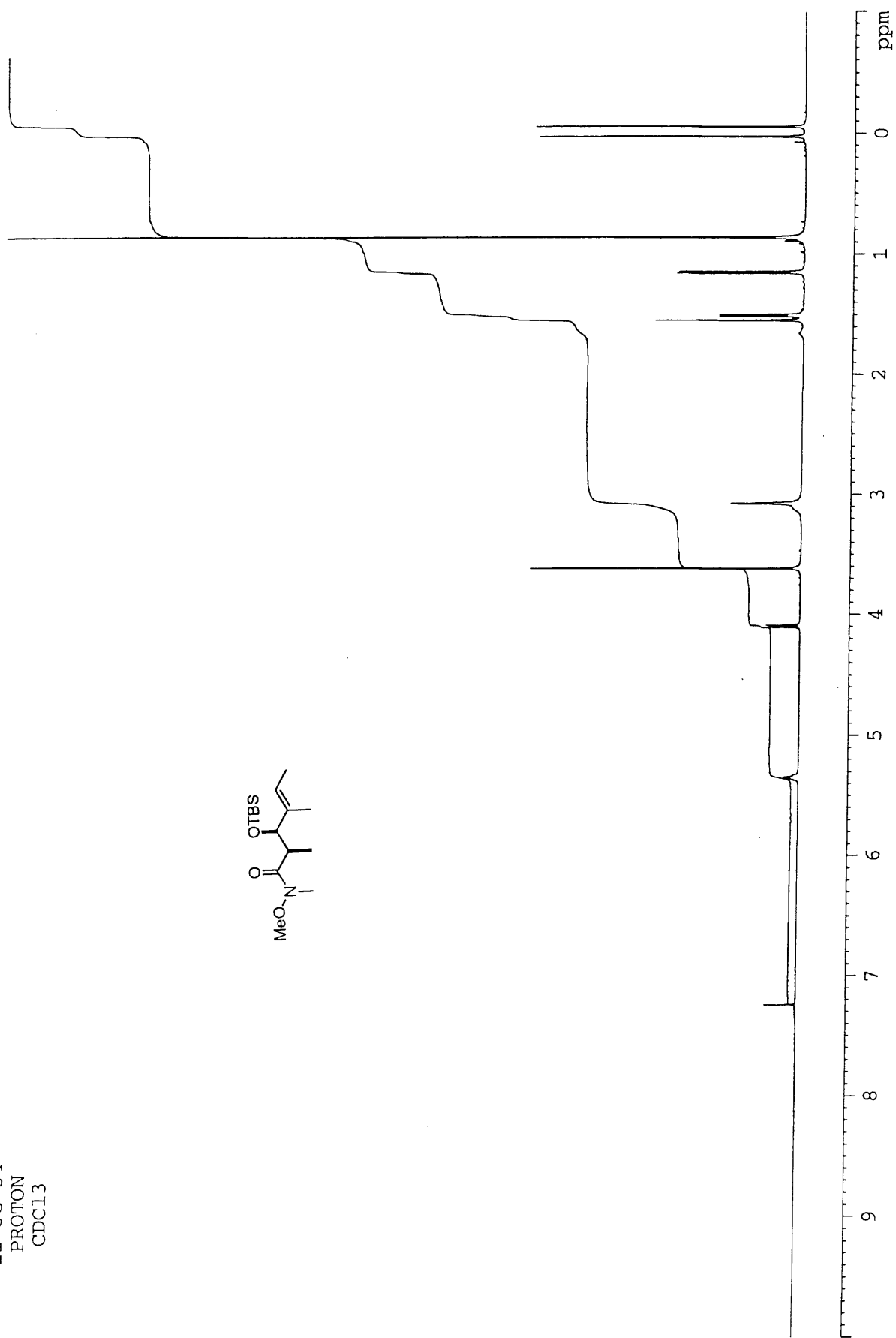


03201004: Scan Avg 24-25 (5.40 - 5.63 min)  
Base: 176.00 Int: 6.37716e+006 Sample: VG-70SE Positive Ion FAB

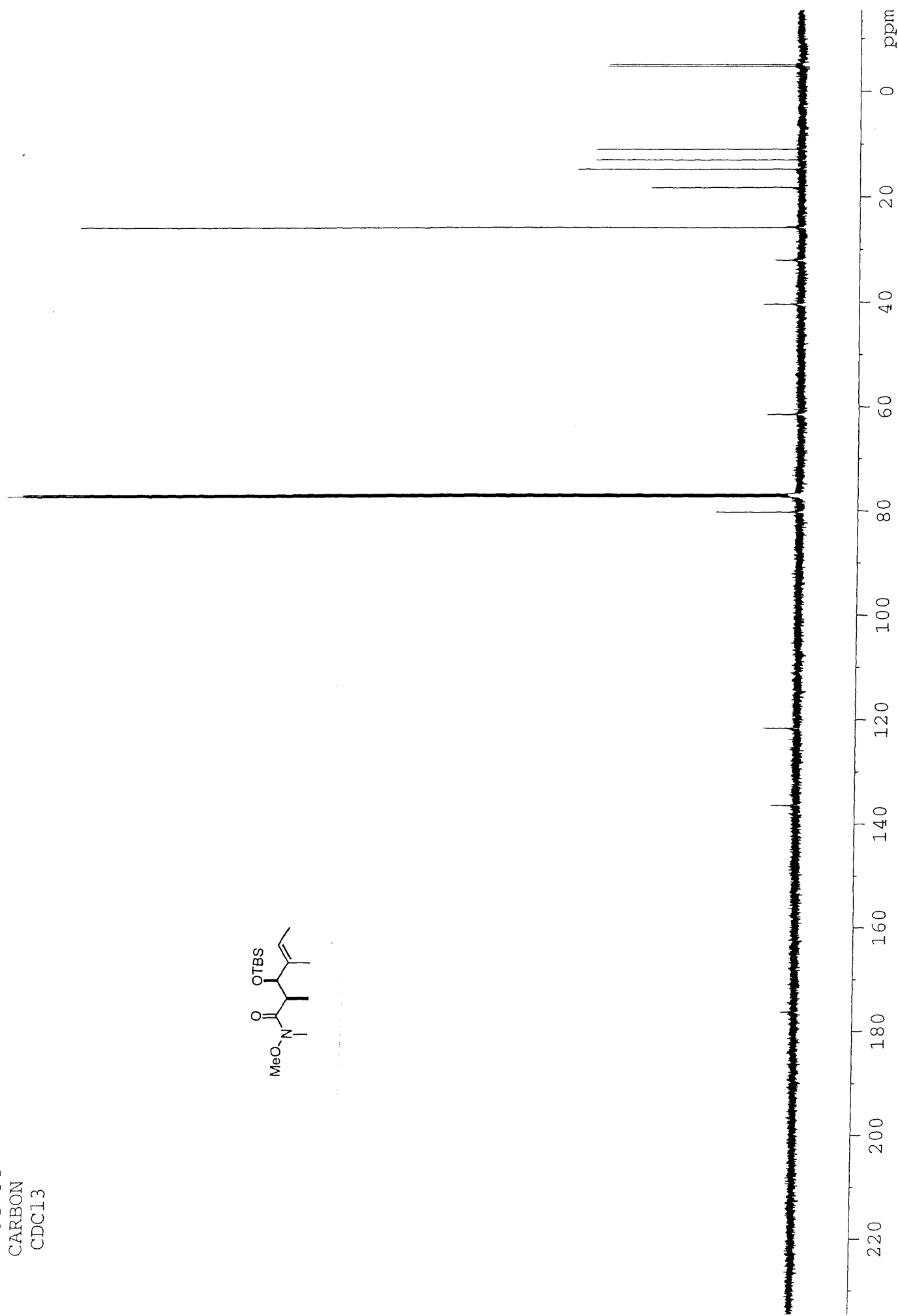
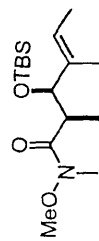


Sample: I-JG-145 (FAB+Na)  
Theoretical Mass: 224.12626 (M+Na)  
Measured Mass: 224.12593 (M+Na)  
Error: 1.44 ppm

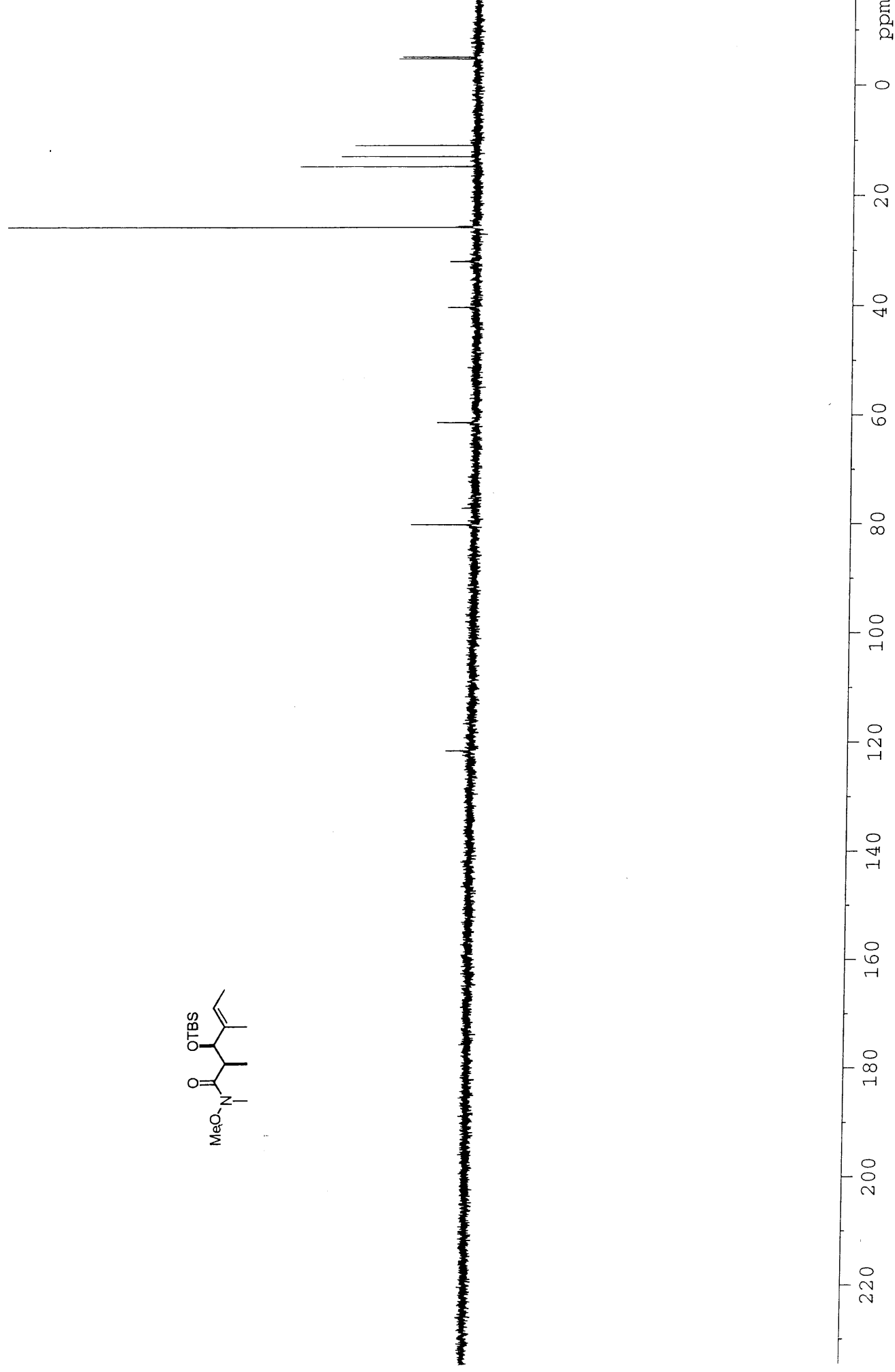
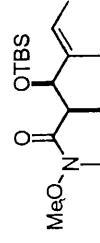


CC(C)C(C(=O)N(C)C)C(OTBS)C=C

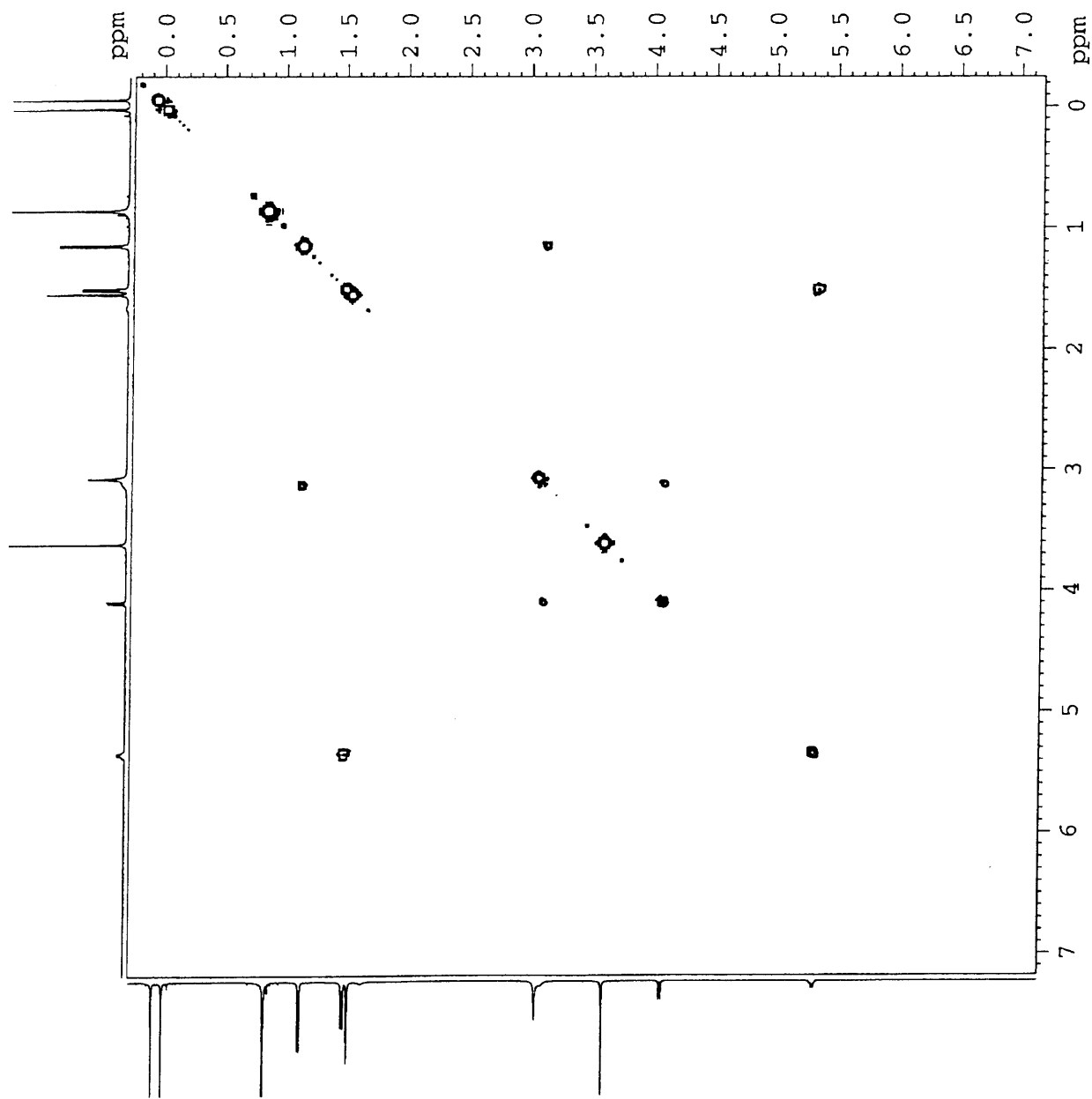
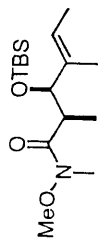
II-JG-54  
CARBON  
CDCl<sub>3</sub>

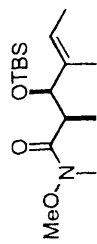


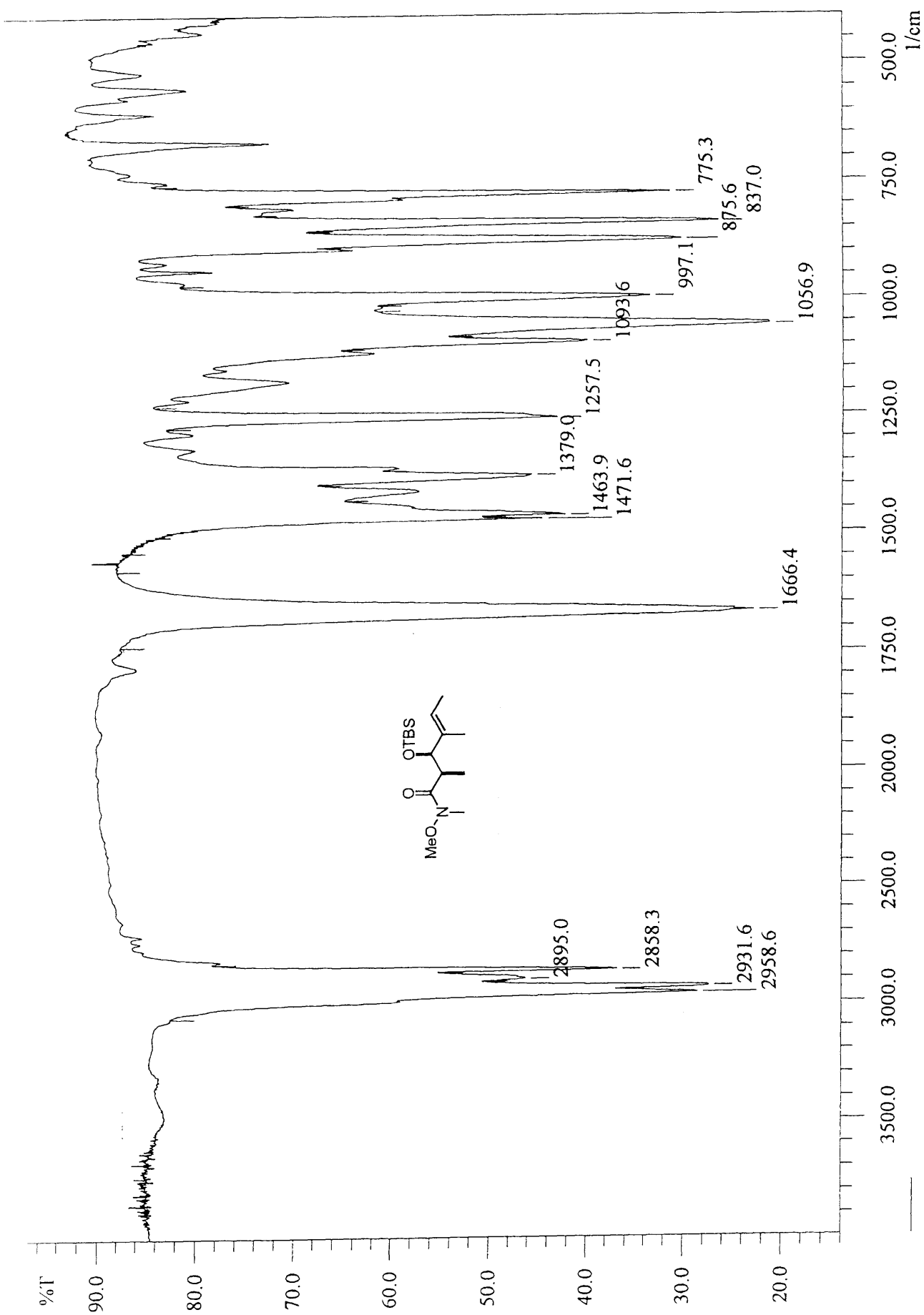
LI-JG-54c  
DEPT  
CDCl3



II-JG-54  
COSY  
CDCl3

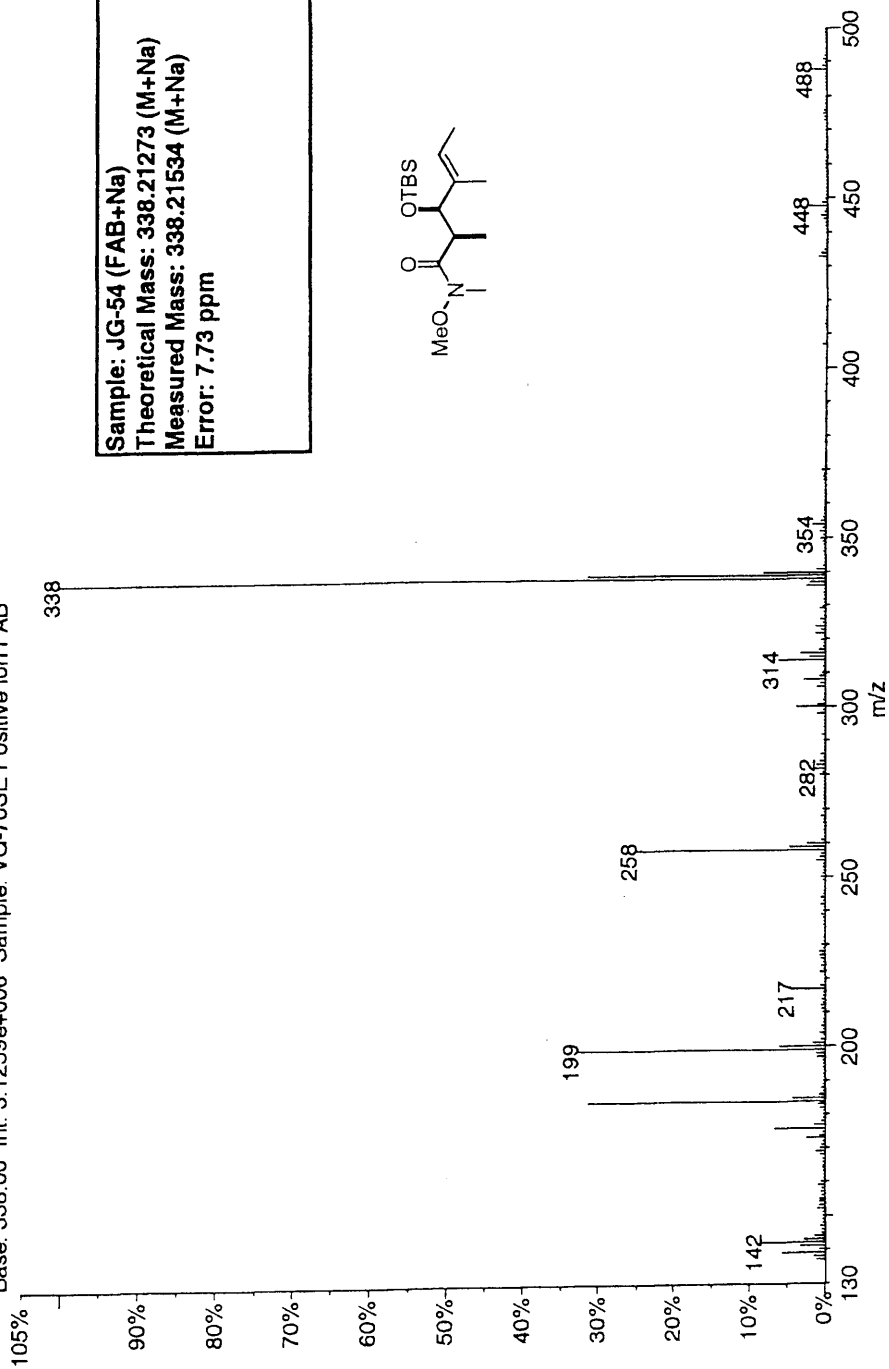




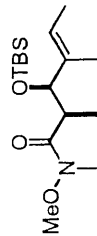




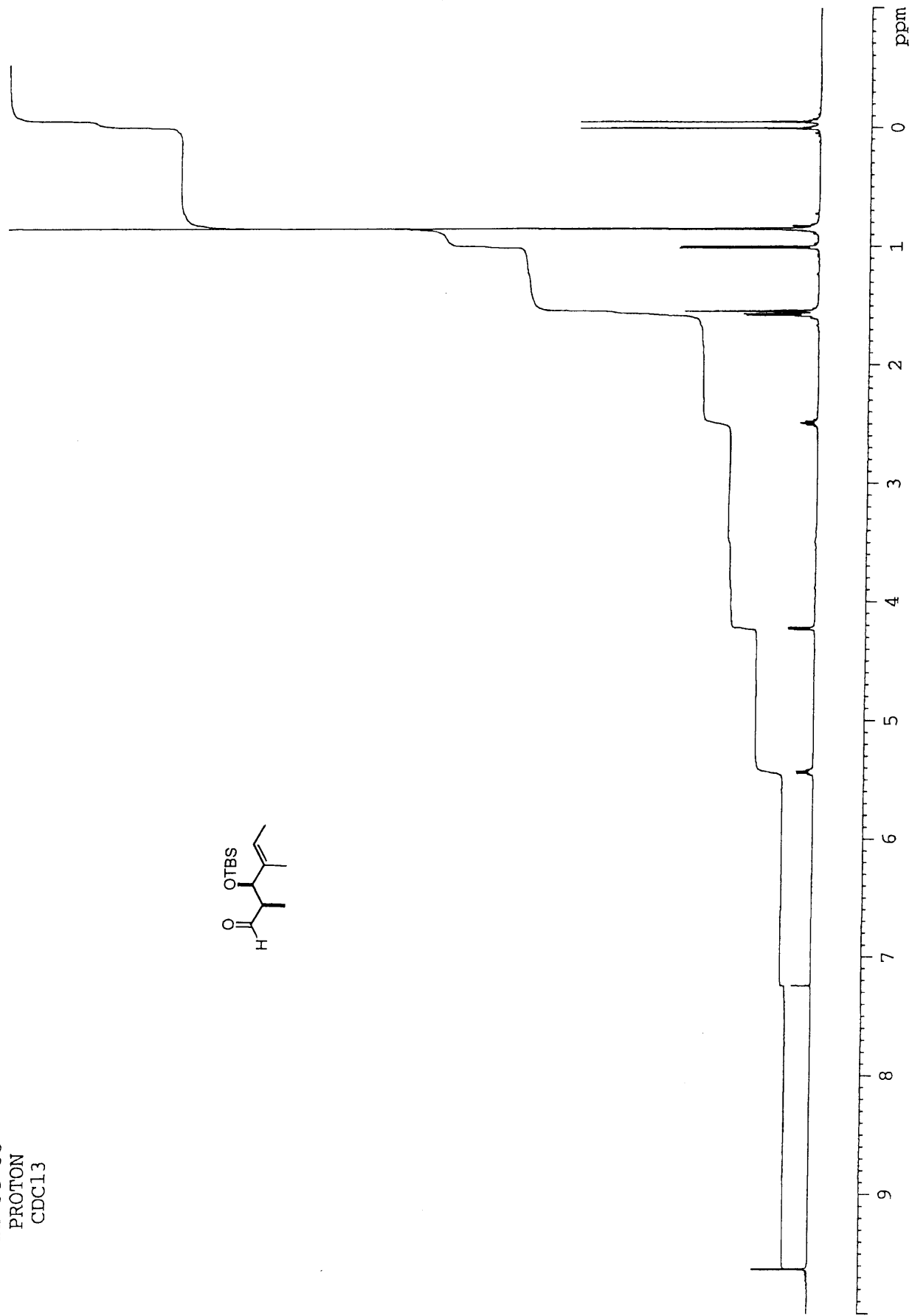
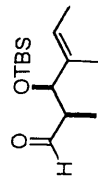
03201004: Scan Avg 37-38 (8.43 - 8.67 min)  
Base: 338.00 Int: 3.1259e+006 Sample: VG-70SE Positive Ion FAB



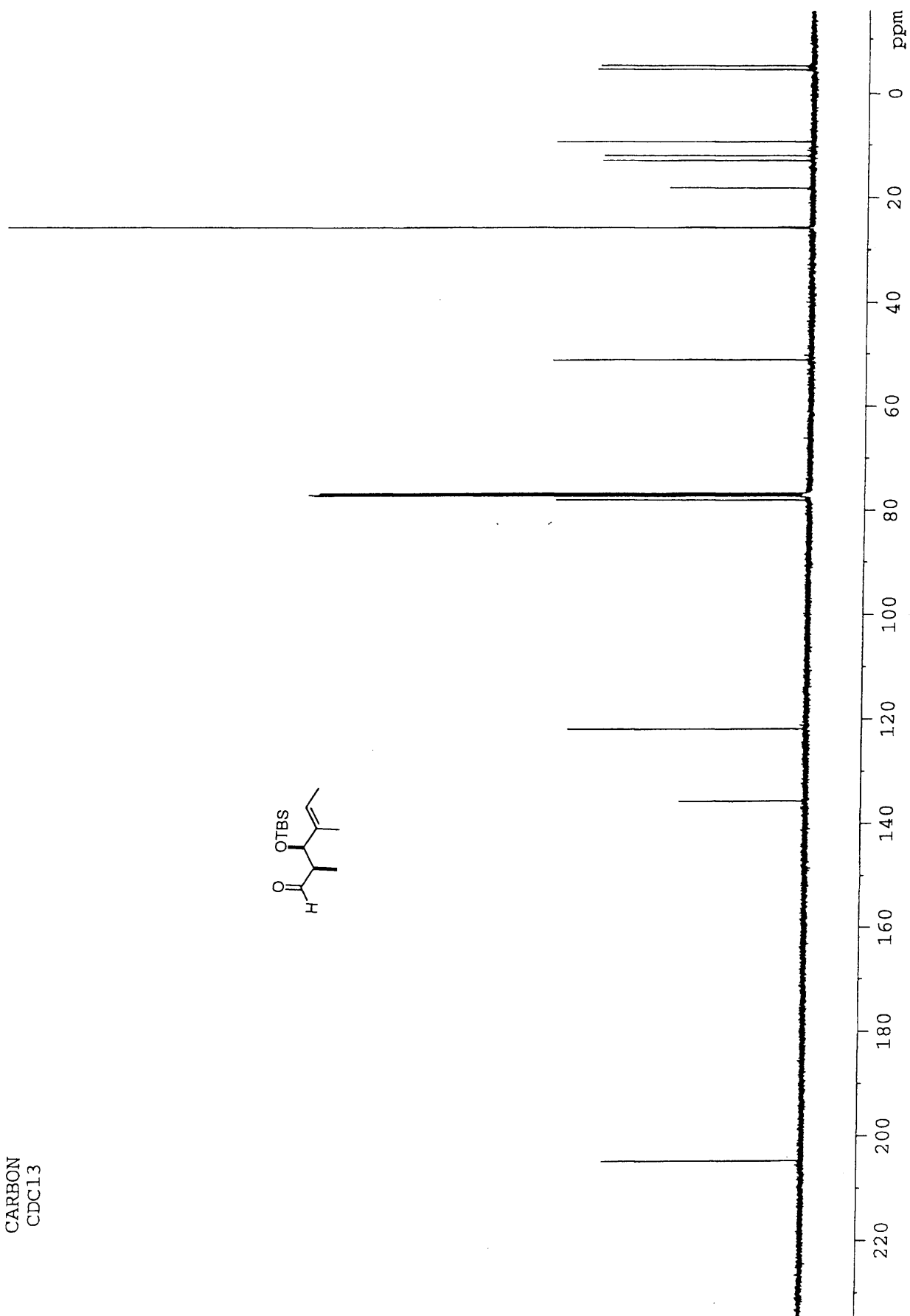
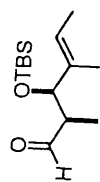
Sample: JG-54 (FAB+Na)  
Theoretical Mass: 338.21273 (M+Na)  
Measured Mass: 338.21534 (M+Na)  
Error: 7.73 ppm

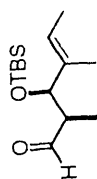


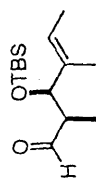
II-JG-55  
PROTON  
CDCl<sub>3</sub>

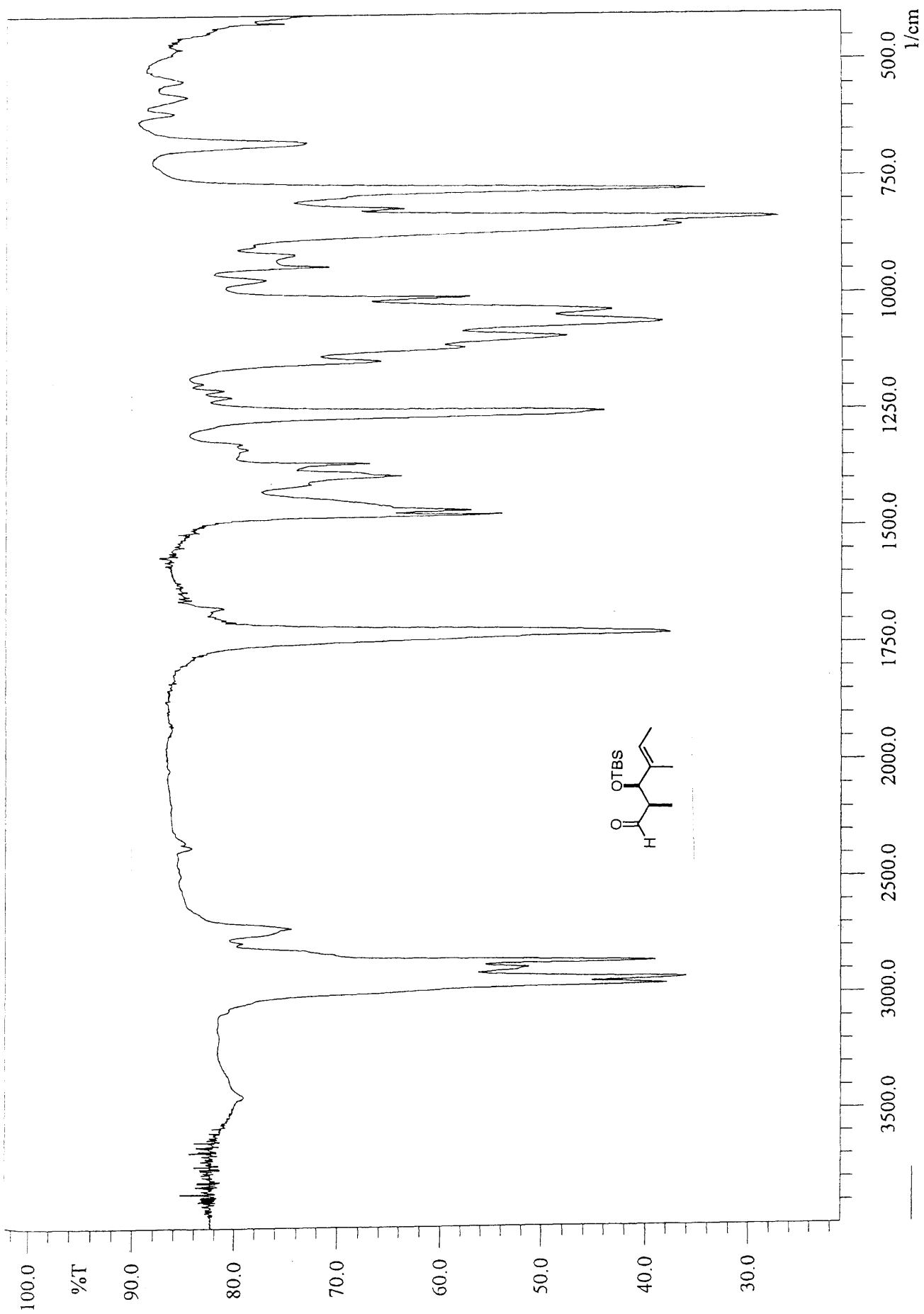


II-JG-55  
CARBON  
CDC13

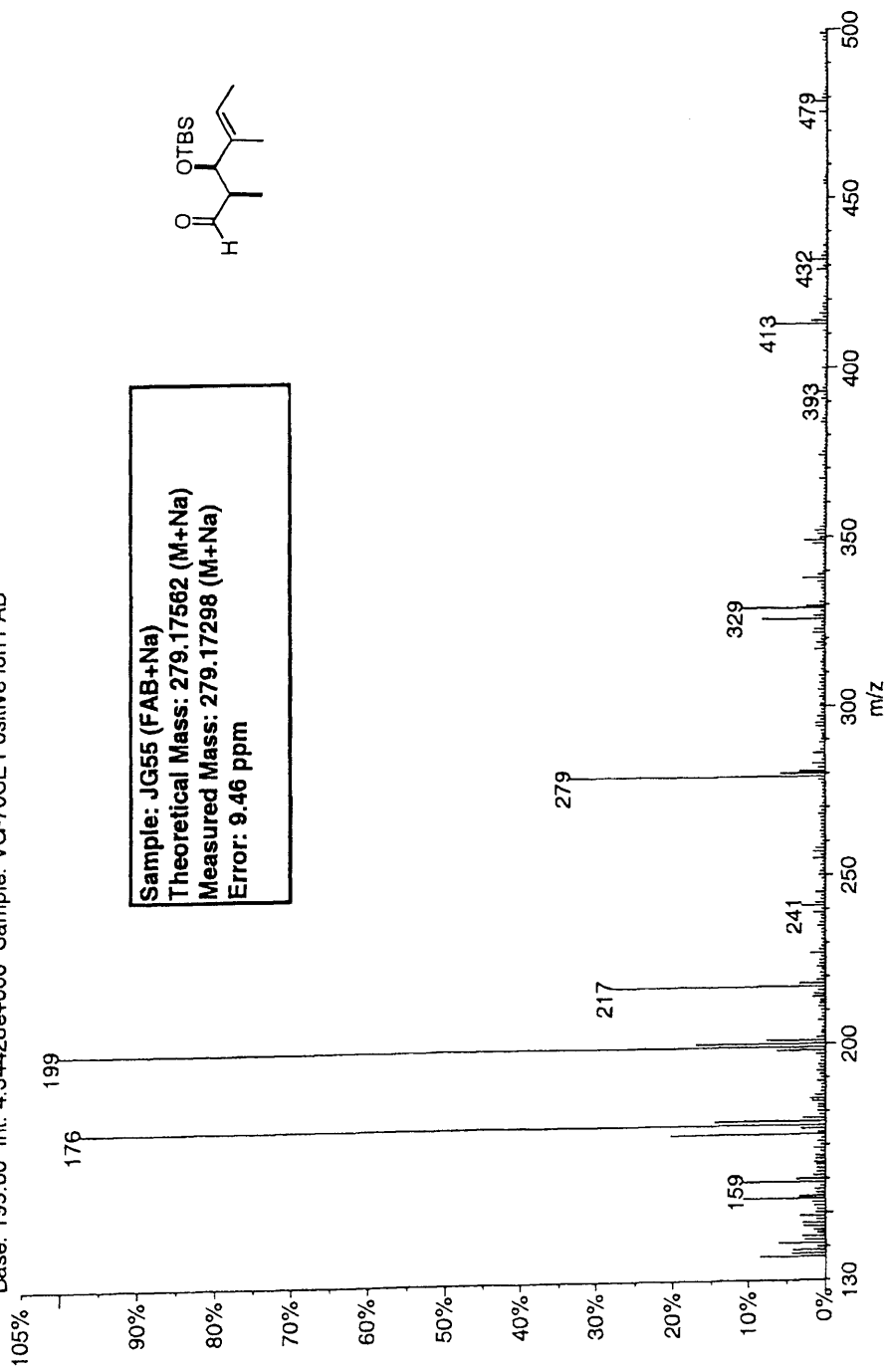




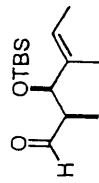




03201004: Scan 49 (11.23 min)  
Base: 199.00 Int: 4.34428e+006 Sample: VG-70SE Positive Ion FAB



Sample: JG55 (FAB+Na)  
Theoretical Mass: 279.17562 (M+Na)  
Measured Mass: 279.17298 (M+Na)  
Error: 9.46 ppm



III-JG-10

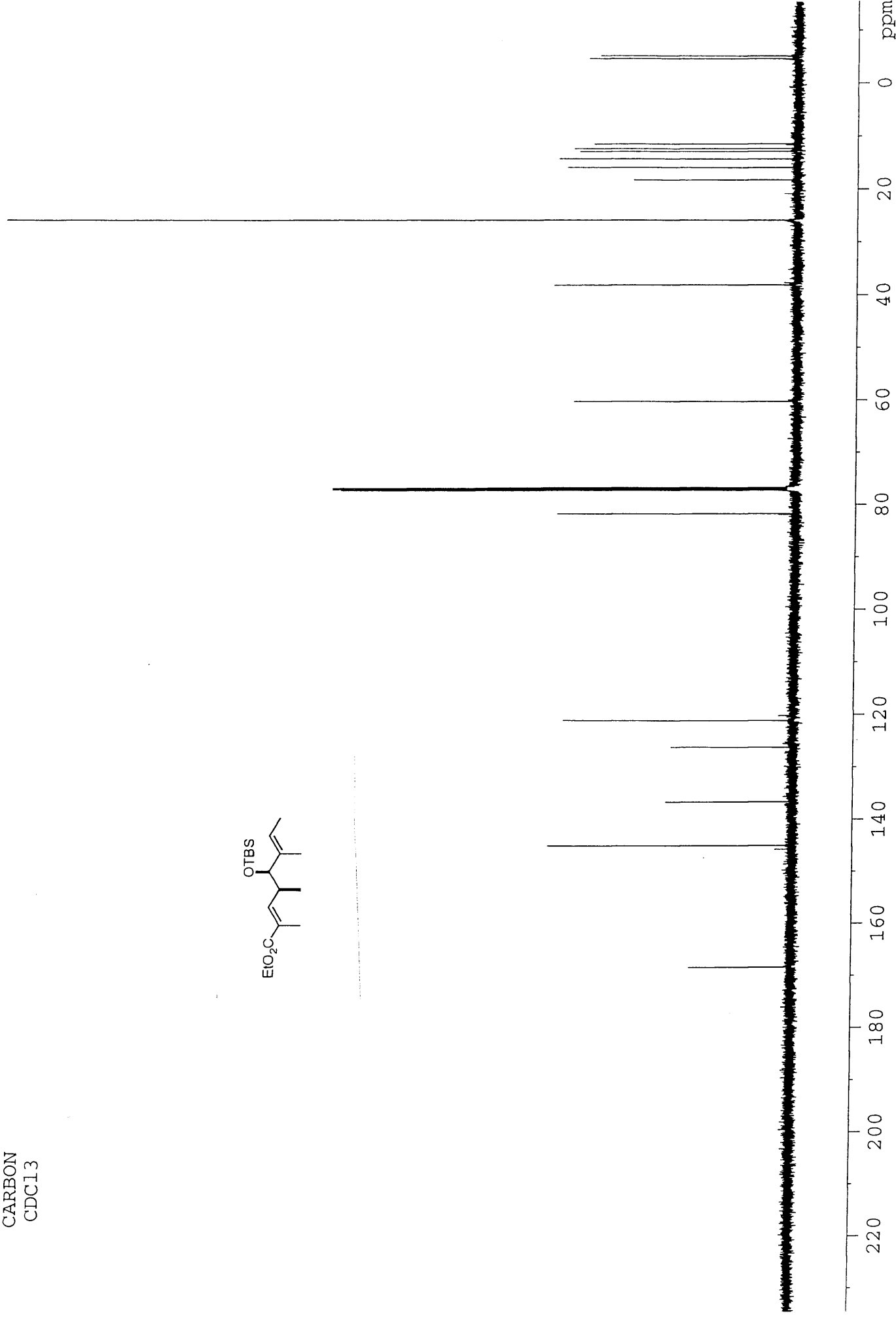
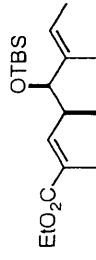
2007

CHAD

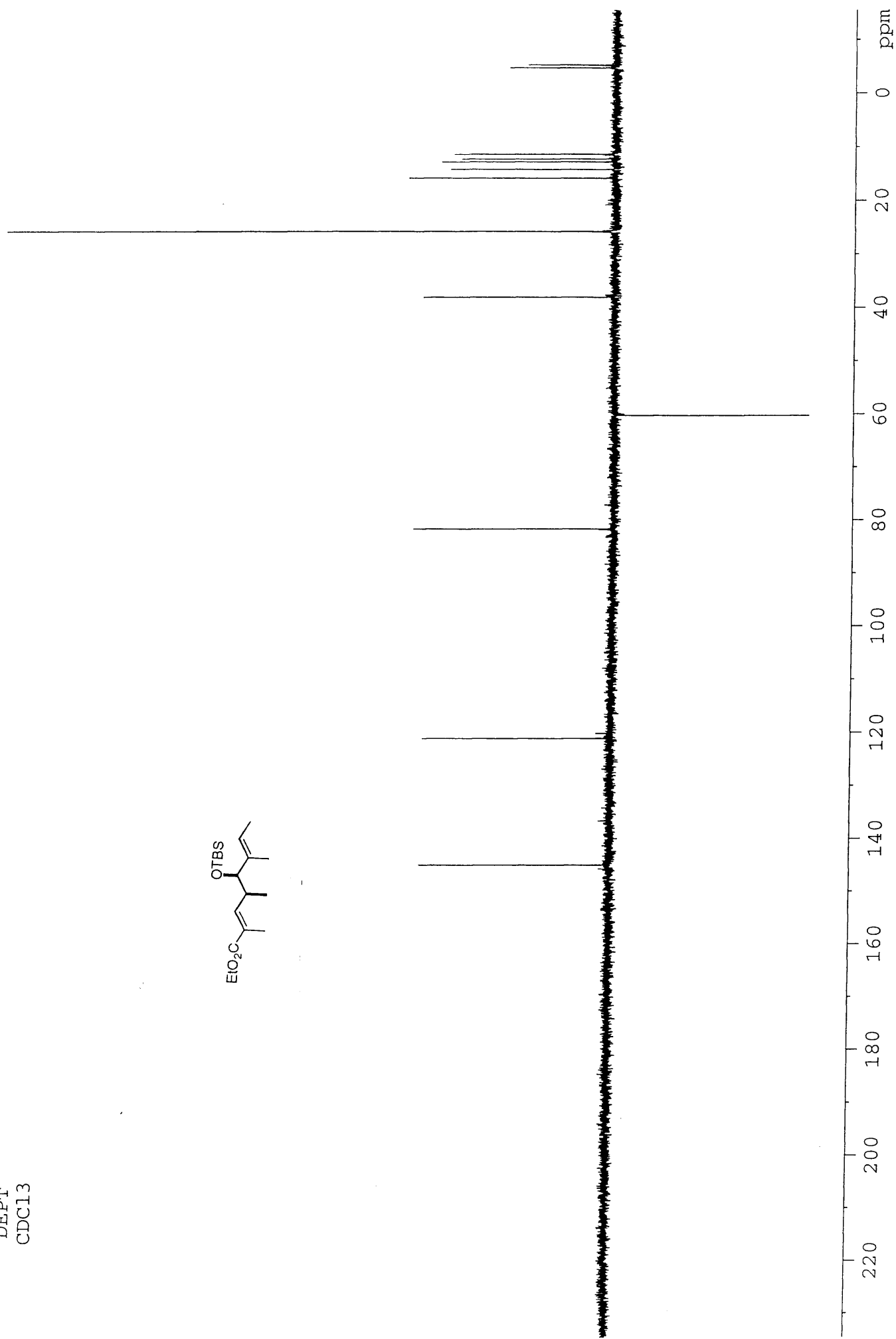
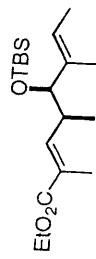




III-JG-10  
CARBON  
CDCl<sub>3</sub>



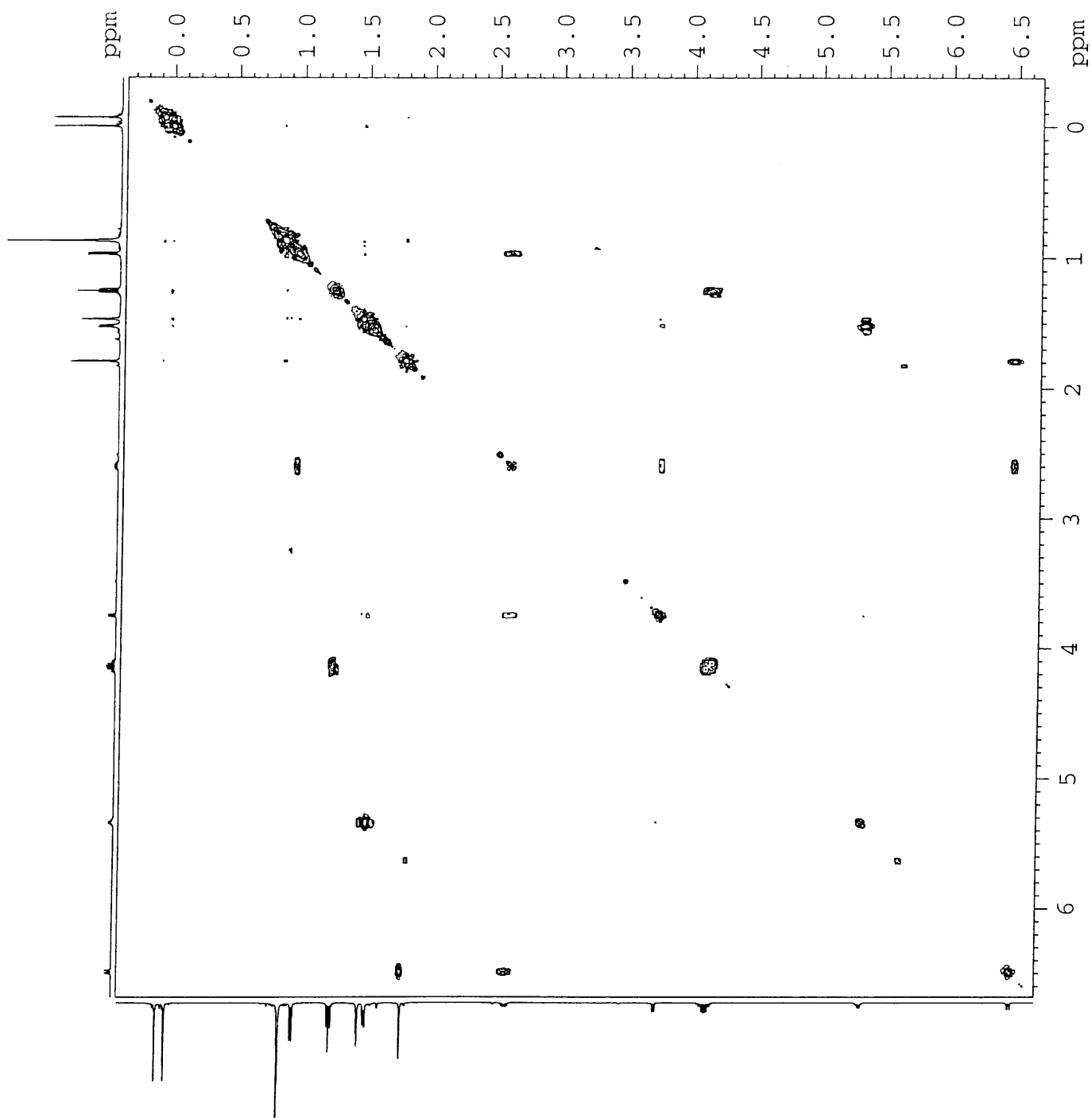
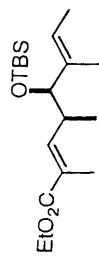
III-JG-10  
DEPT  
CDCl<sub>3</sub>

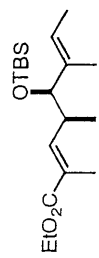


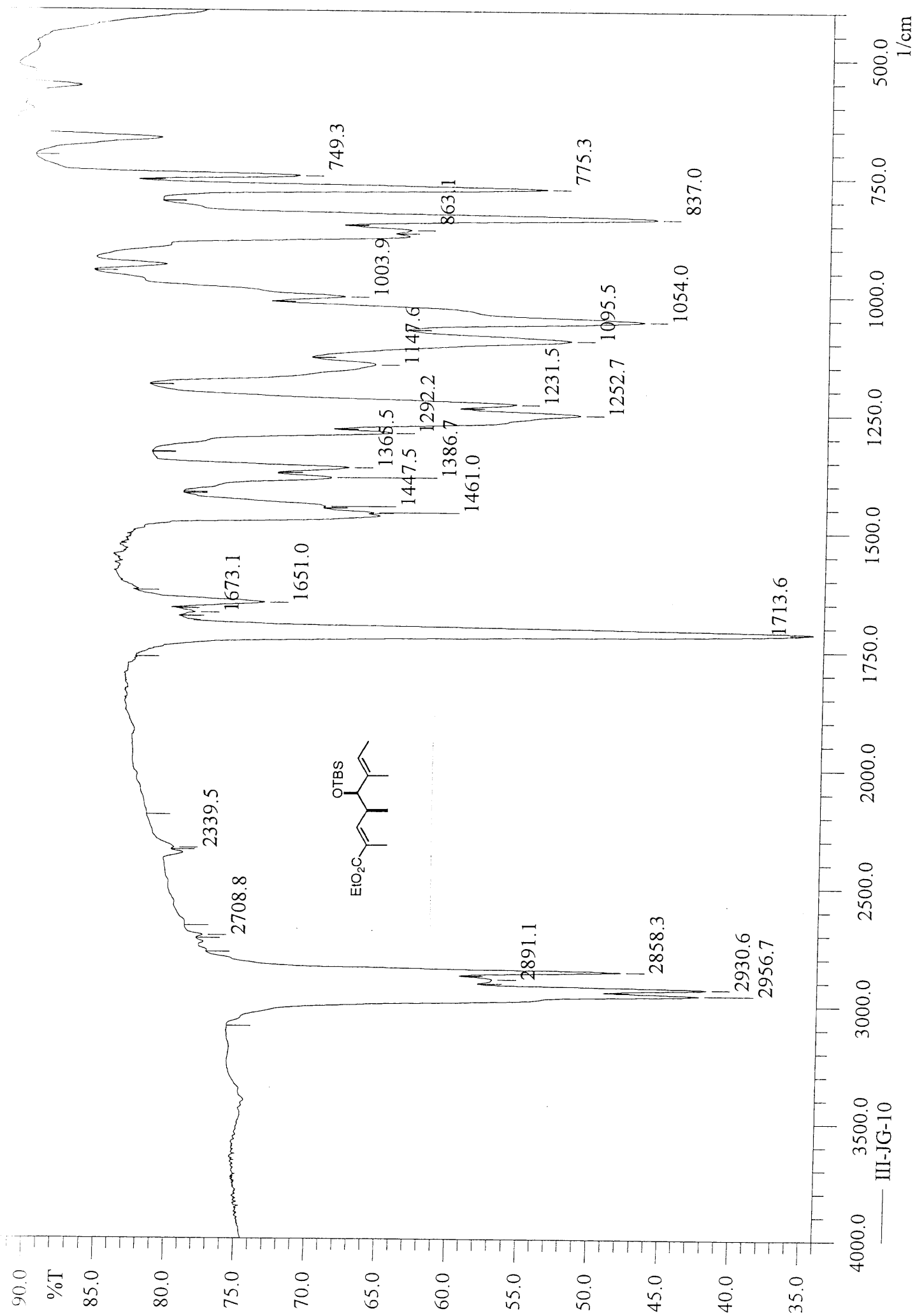
III-JG-10

COSY

CDC13

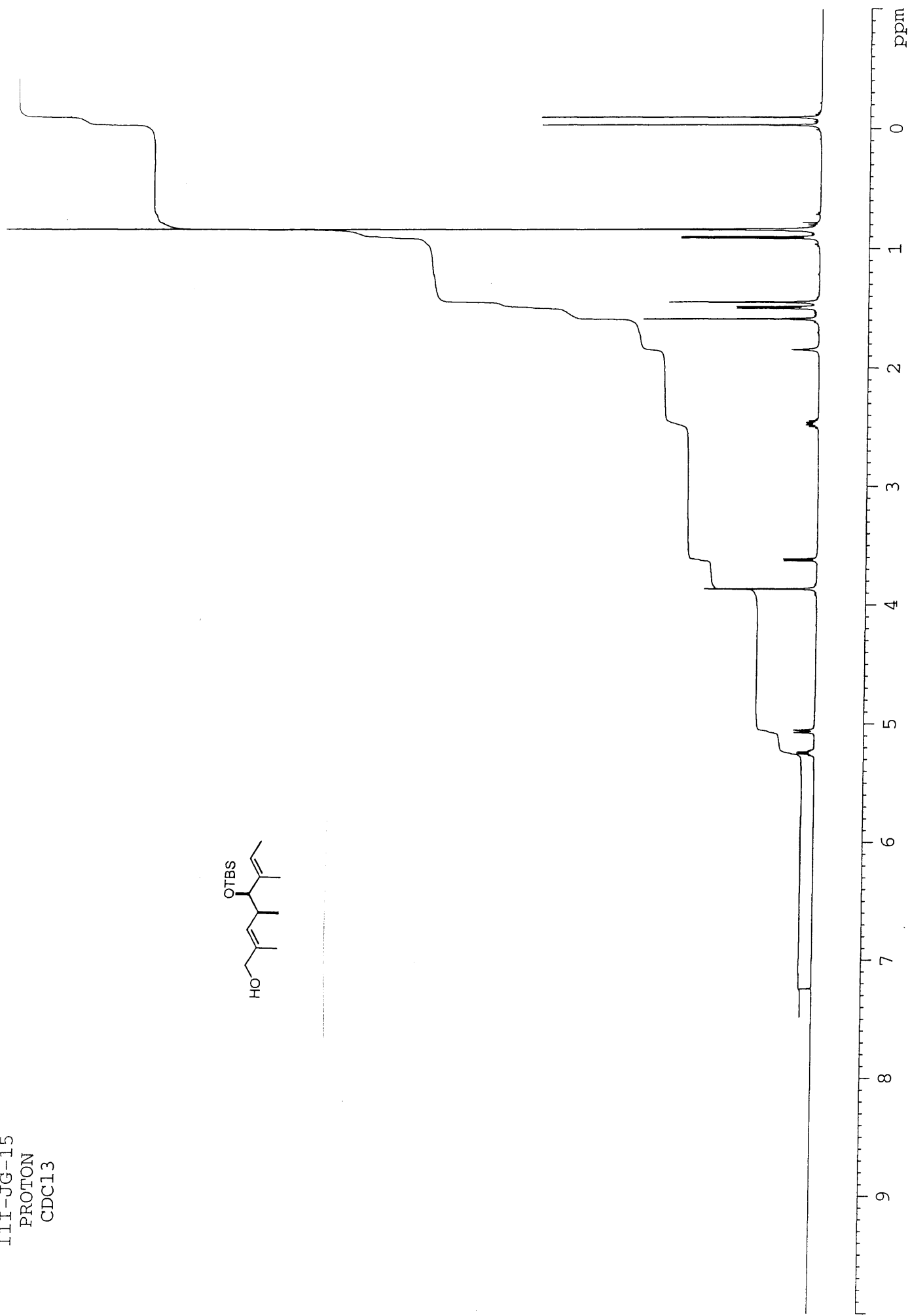
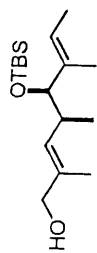




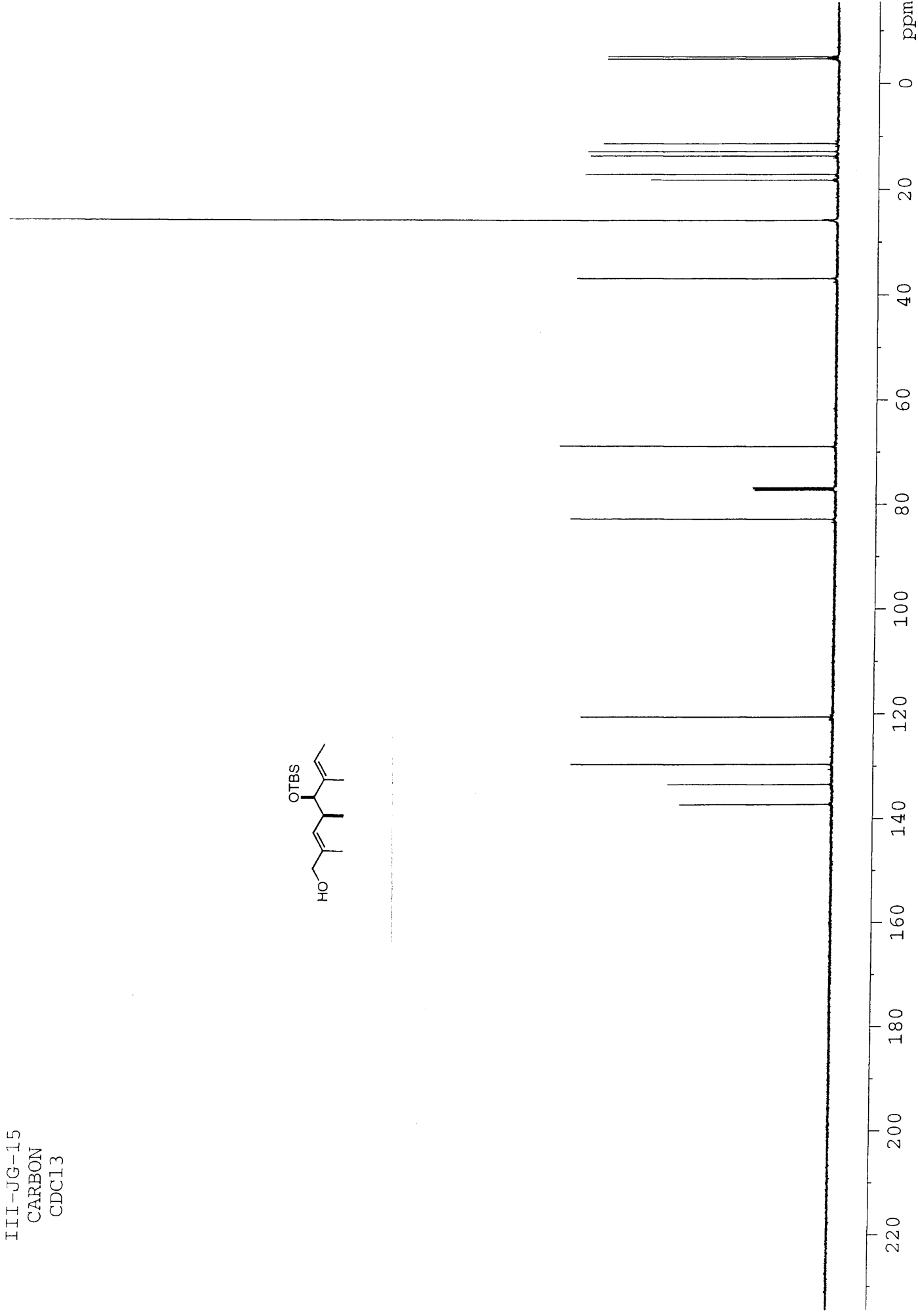
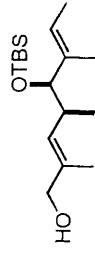




III-JG-15  
PROTON  
CDC13

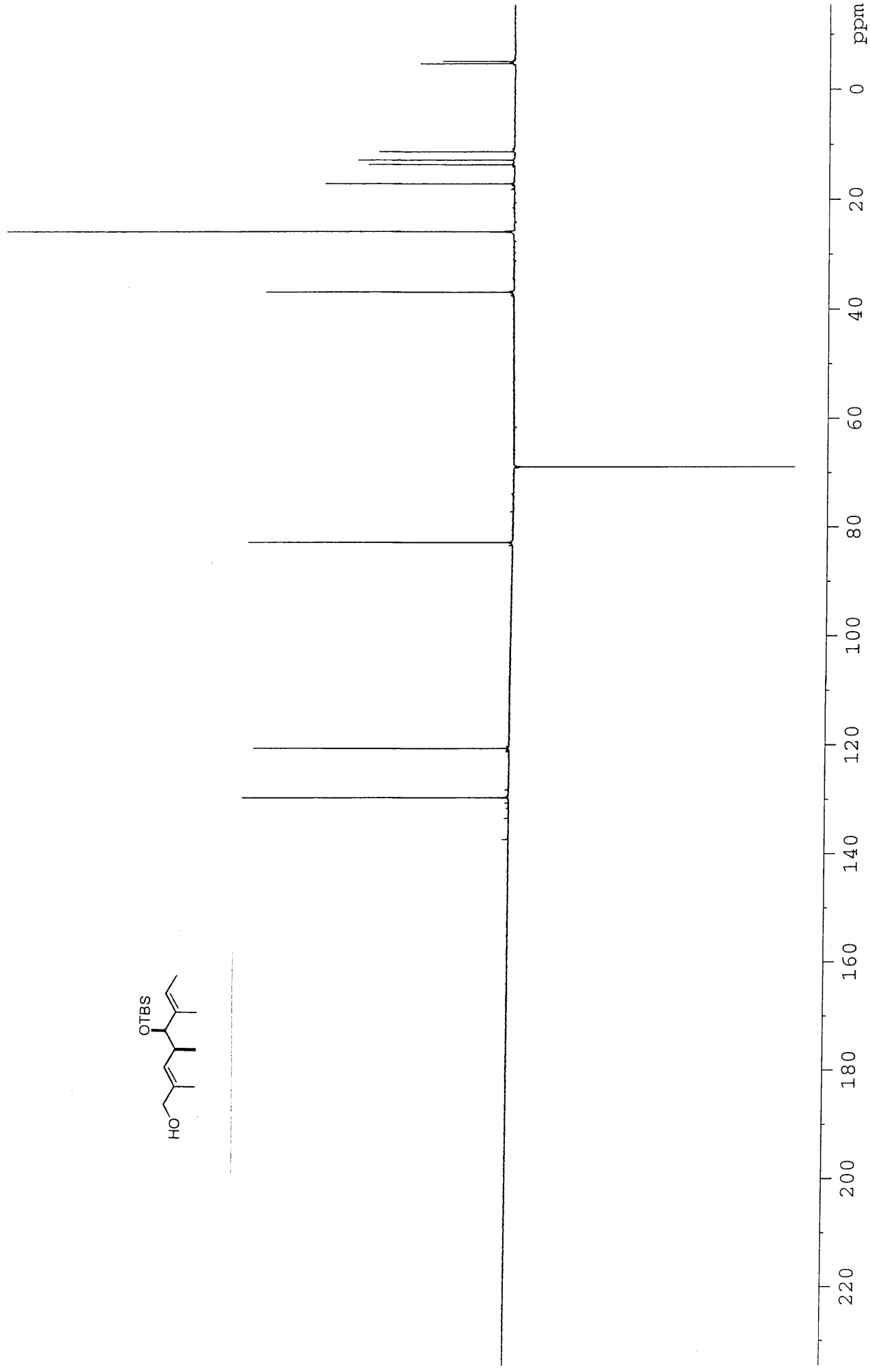
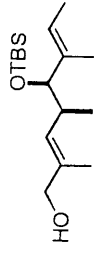


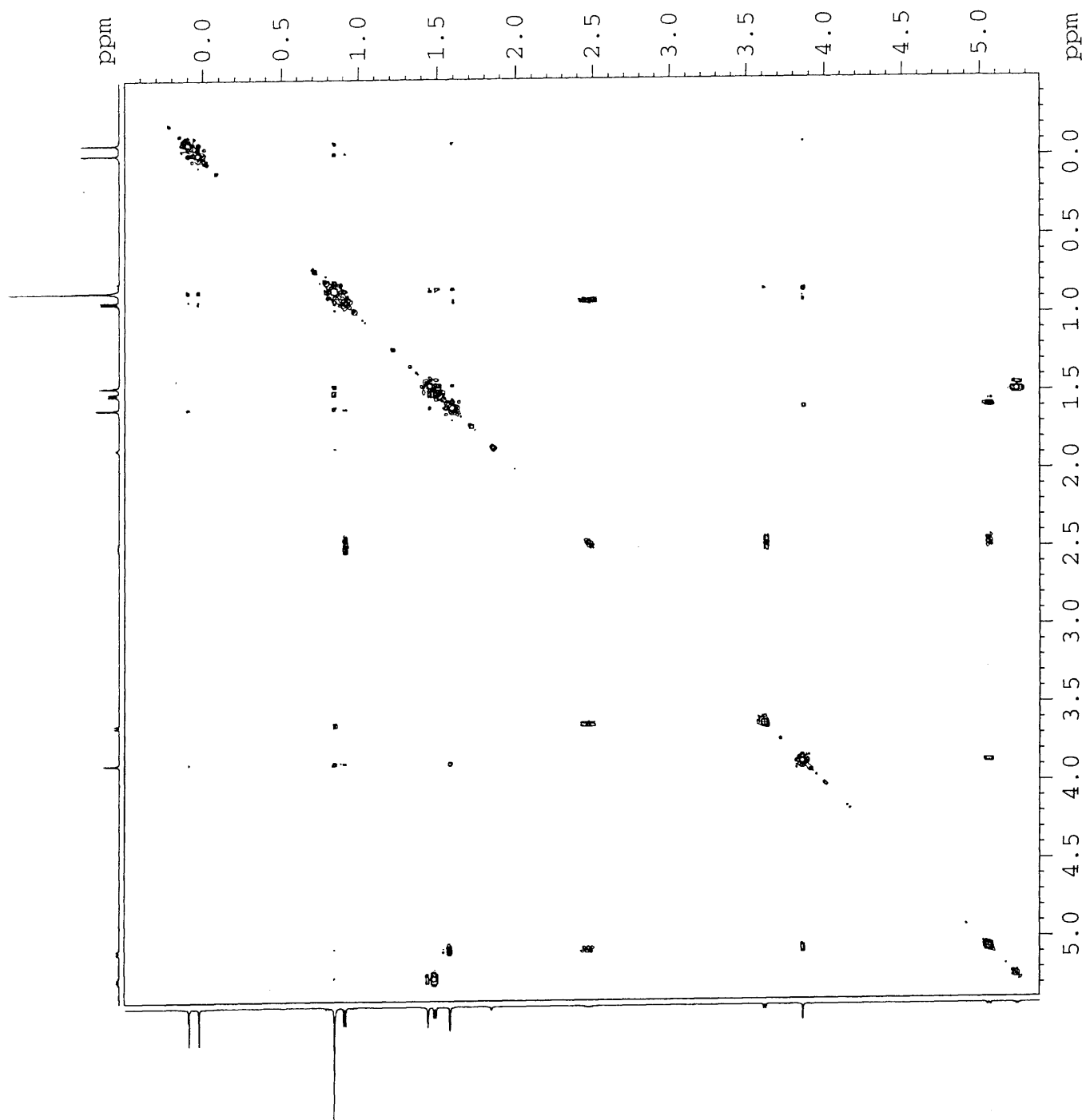
III-JG-15  
CARBON  
CDCl<sub>3</sub>



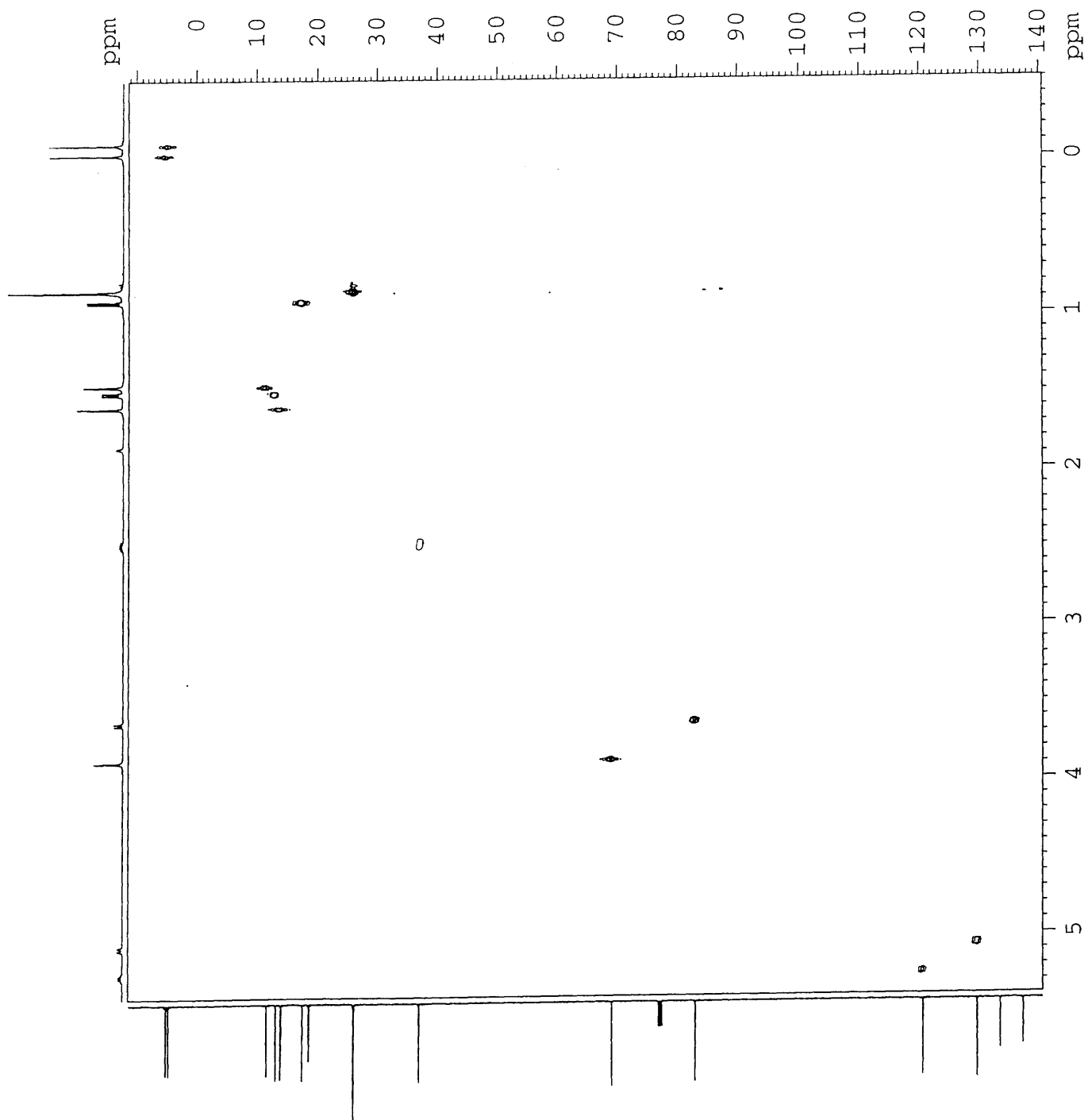
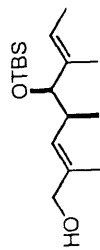


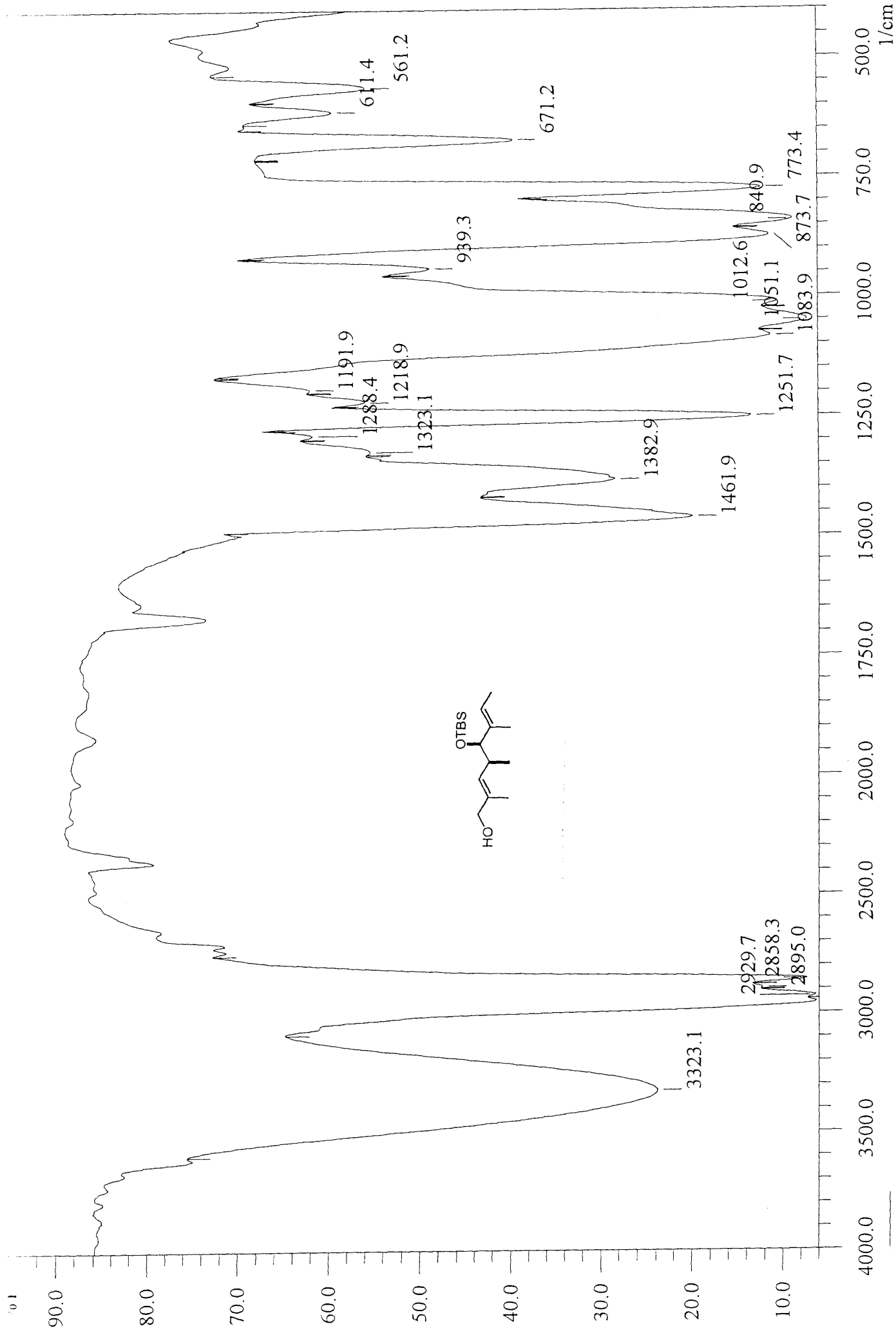
III-JG-15  
DEPT  
CDC13



C=C(C)[C@H](O)C[C@@H](C(=O)OSi(C)(C)C)C=C(C)C

CDC13



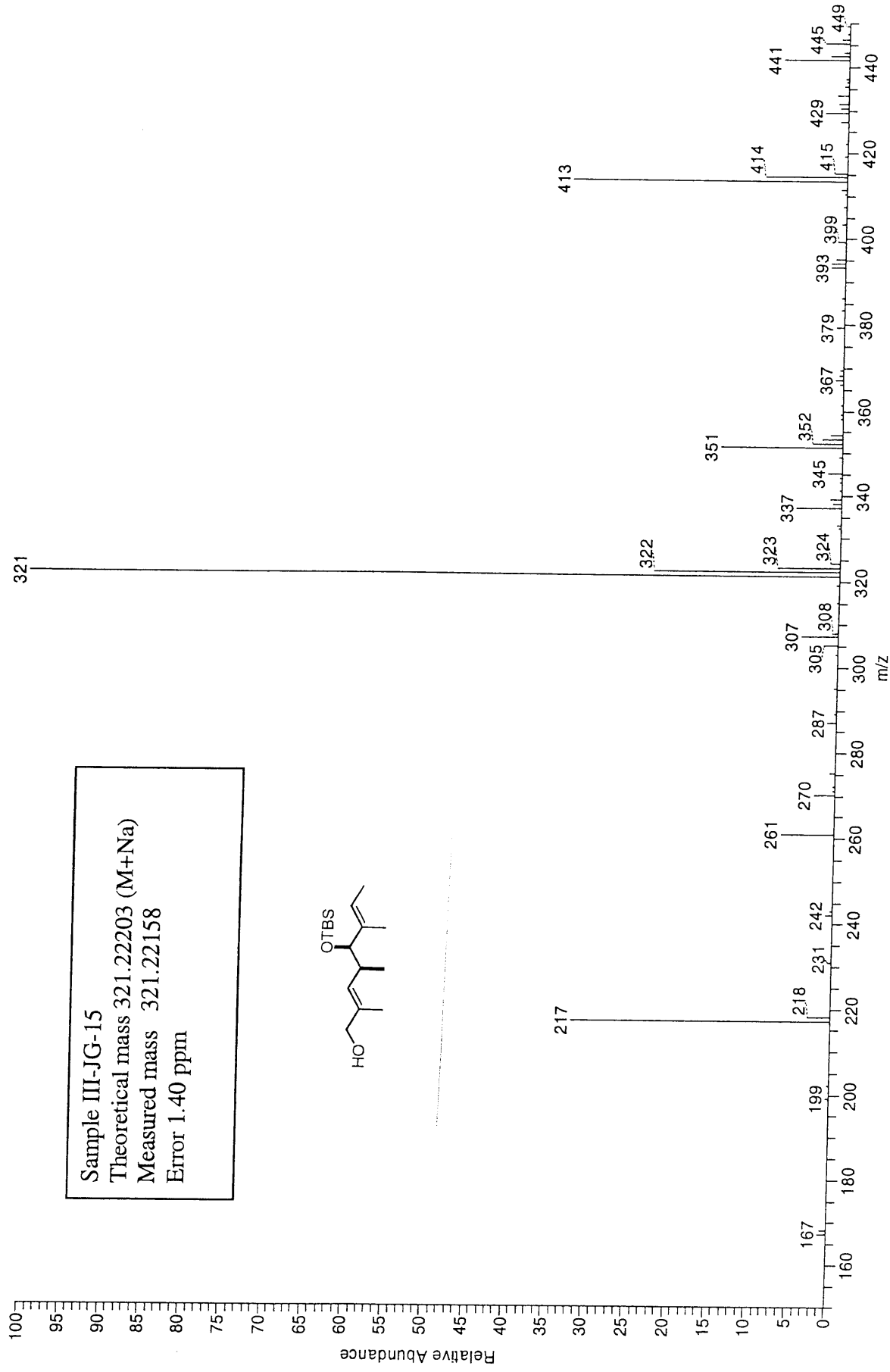
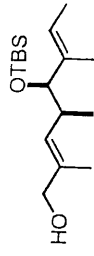


Sample III-JG-15

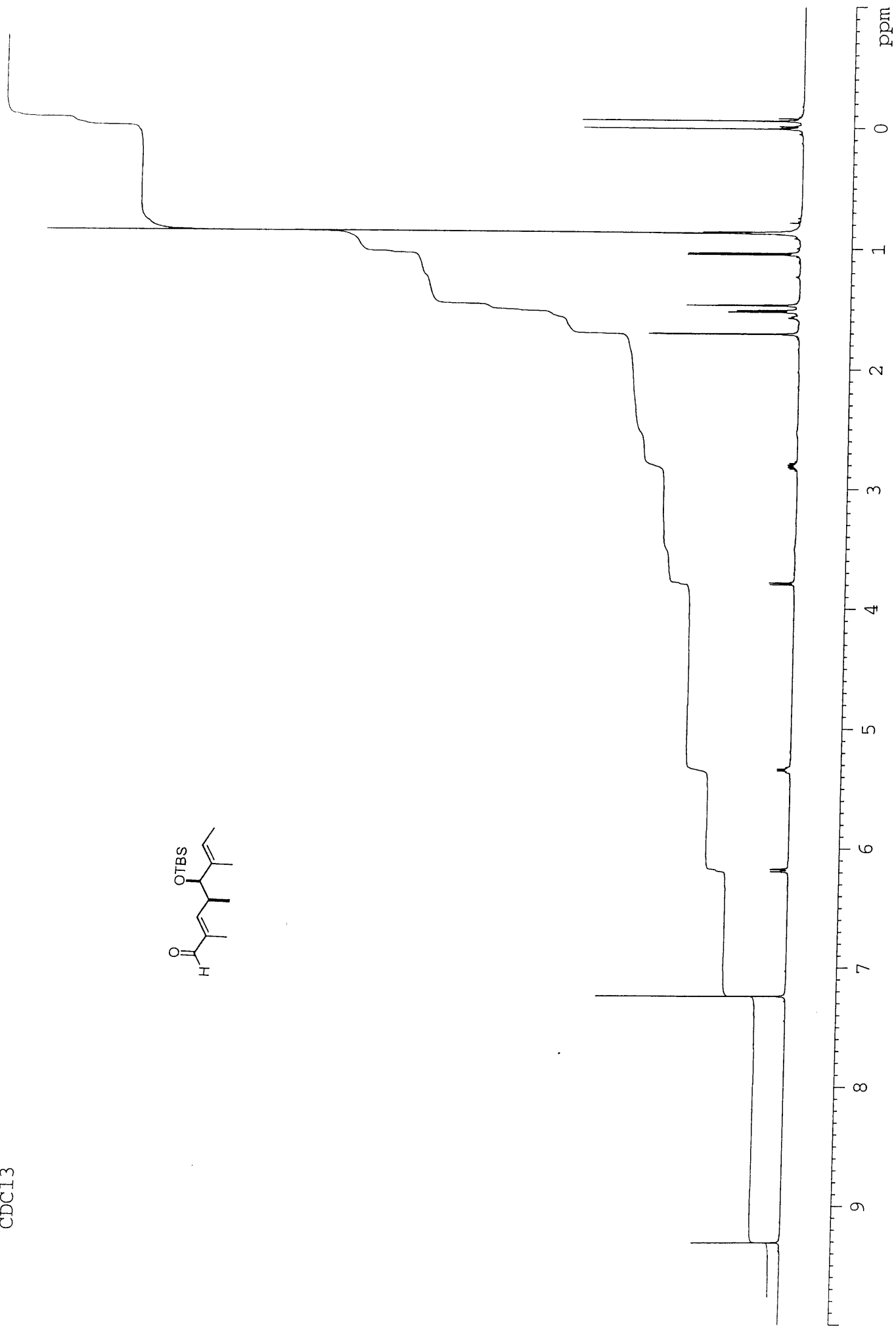
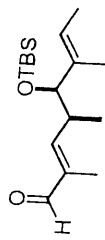
Theoretical mass 321.22203 (M+Na)

Measured mass 321.22158

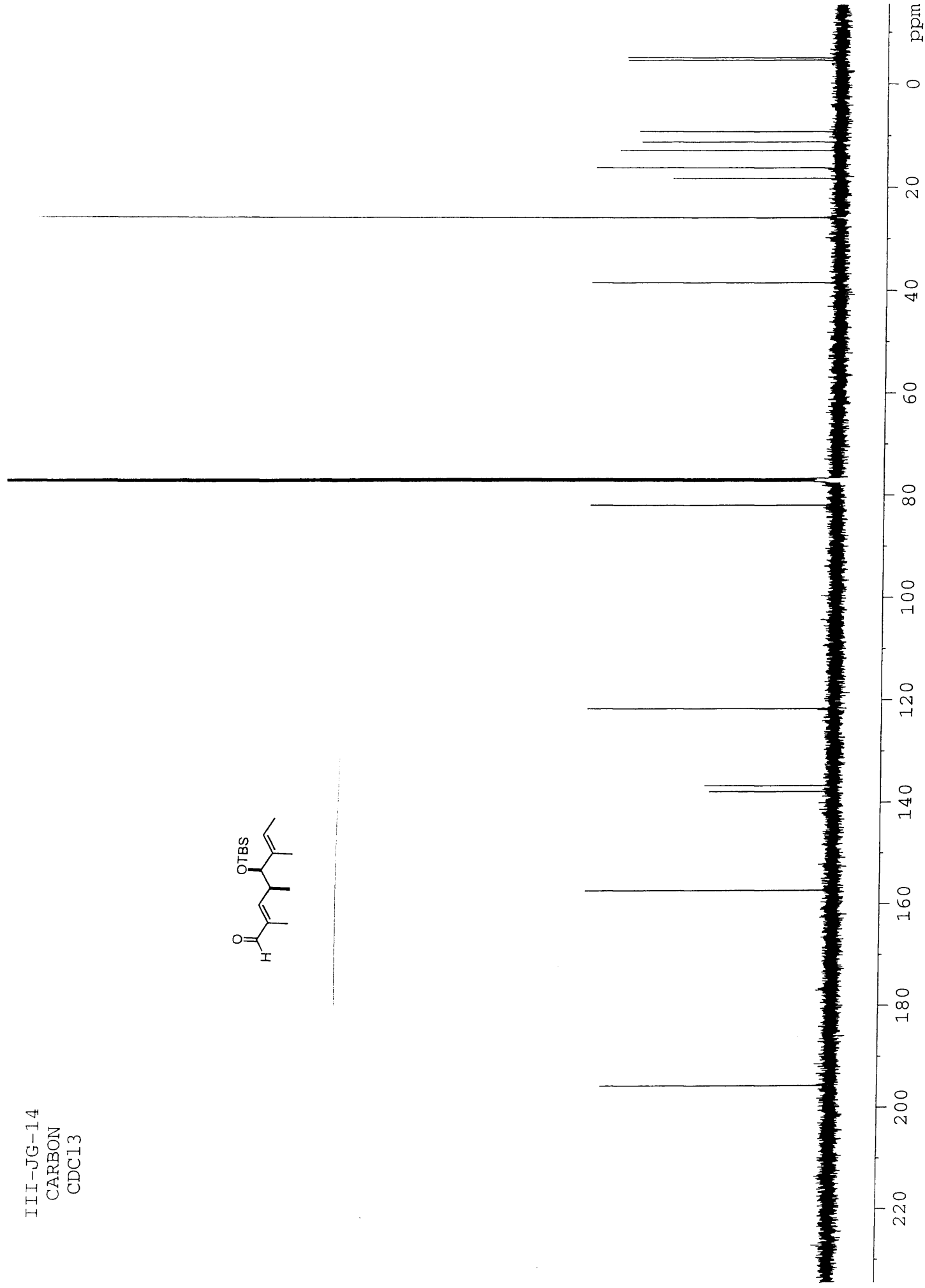
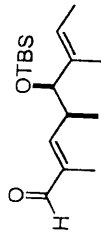
Error 1.40 ppm



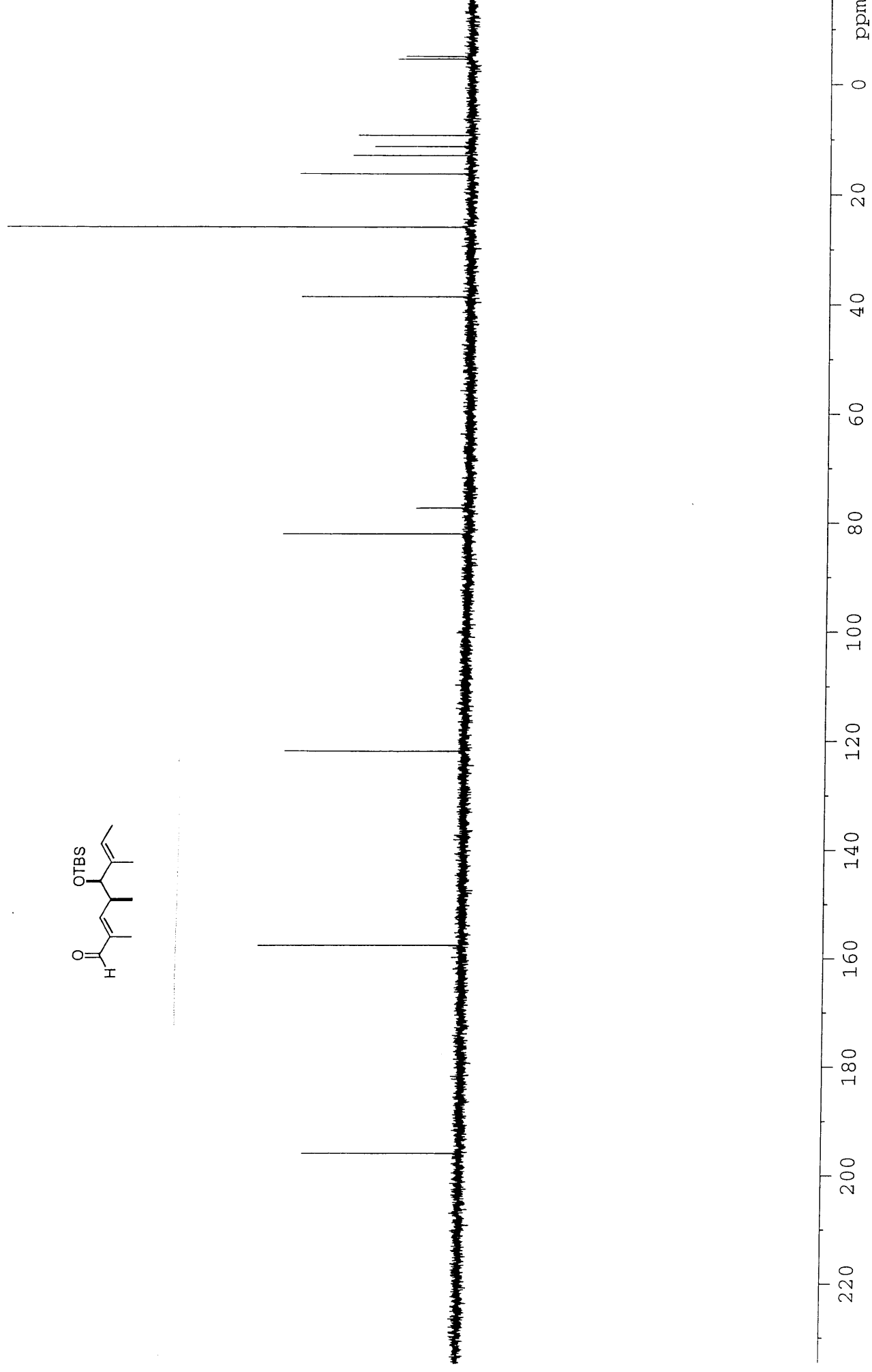
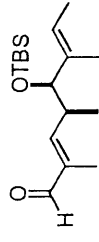
III-JG-14  
PROTON  
CDCl<sub>3</sub>



III-JG-14  
CARBON  
CDCl<sub>3</sub>

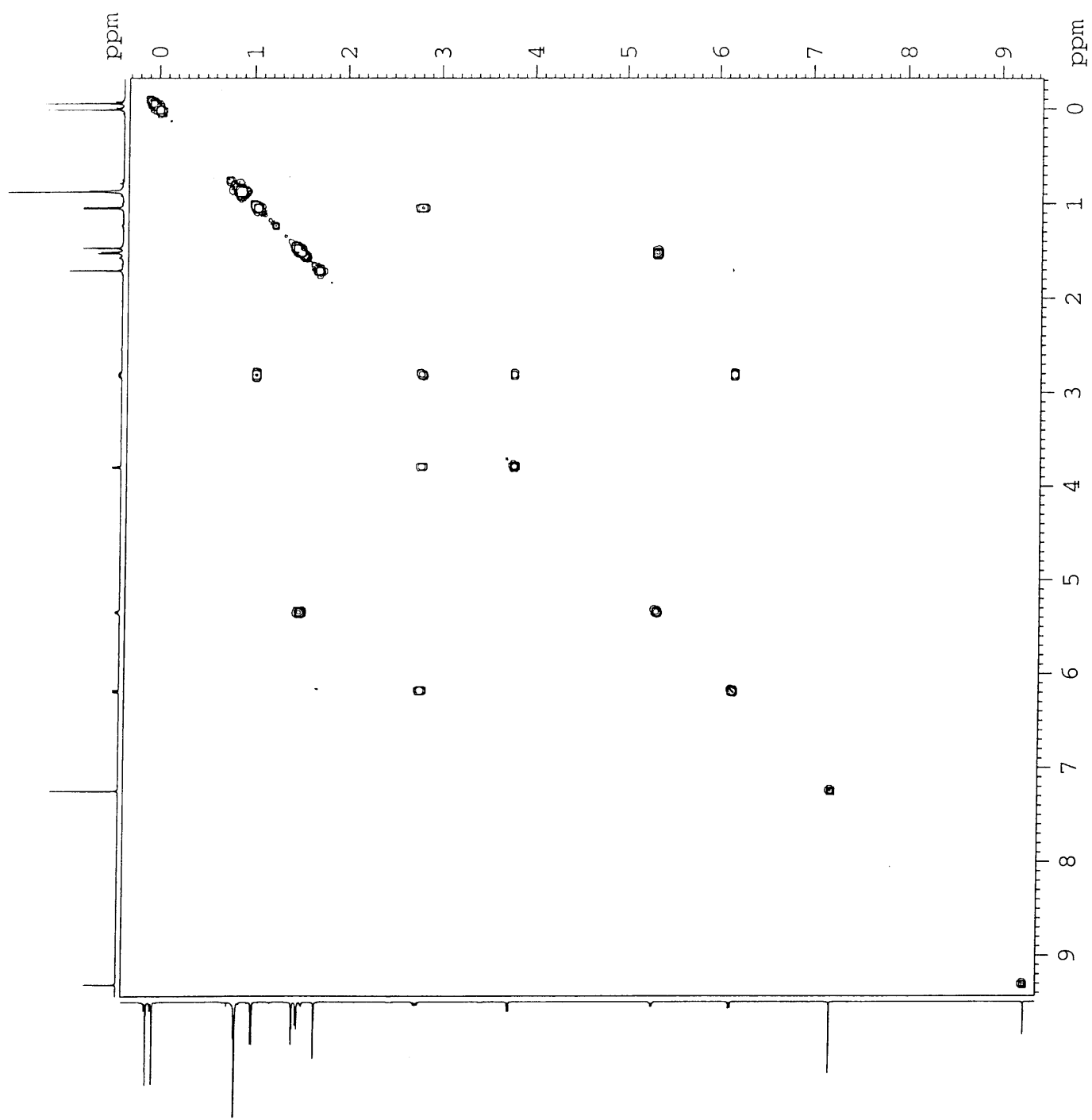
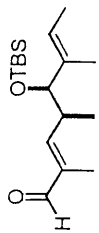


III-JG-14  
DEPT  
CDCl3

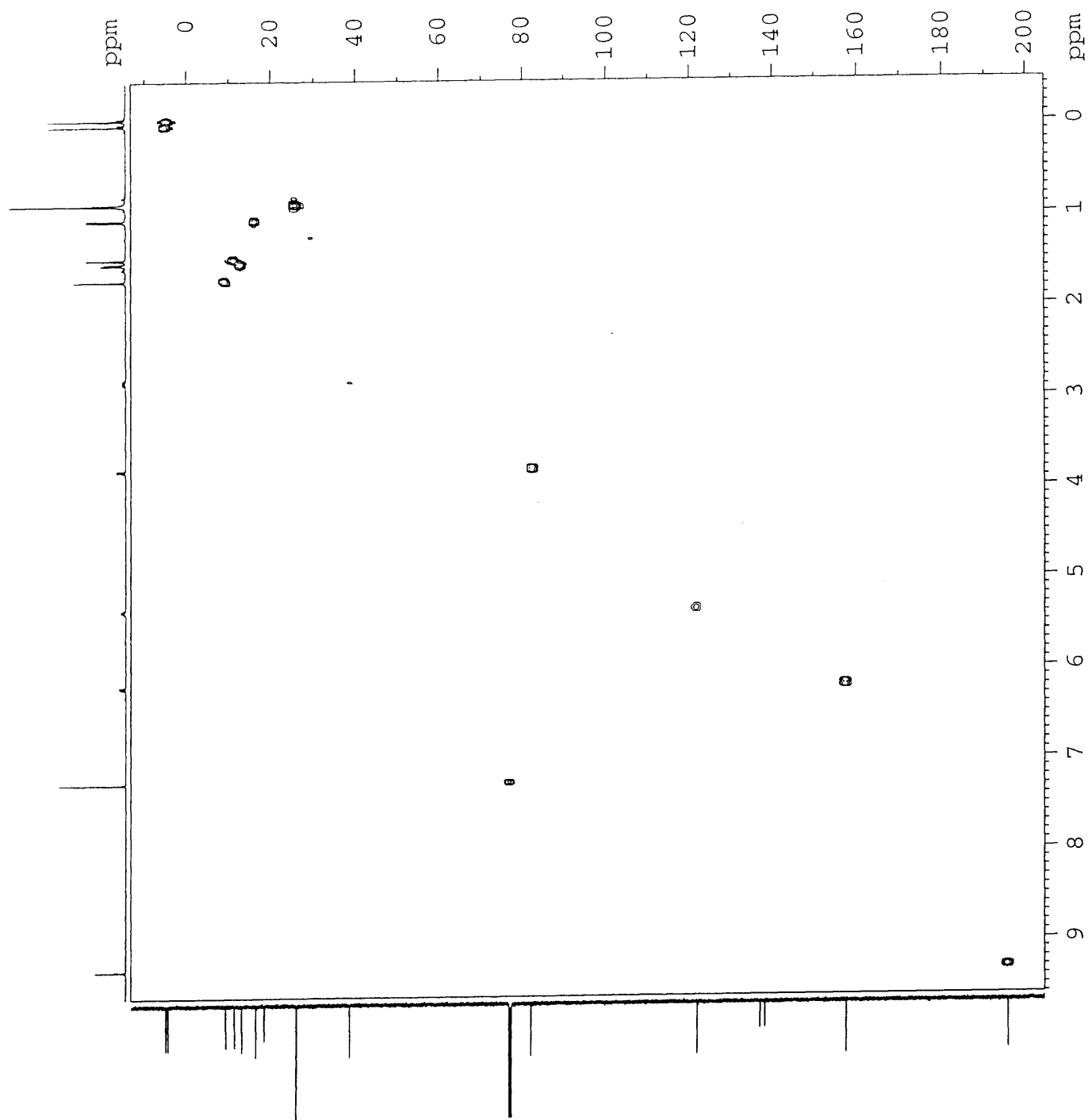
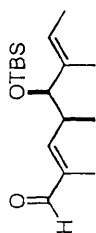


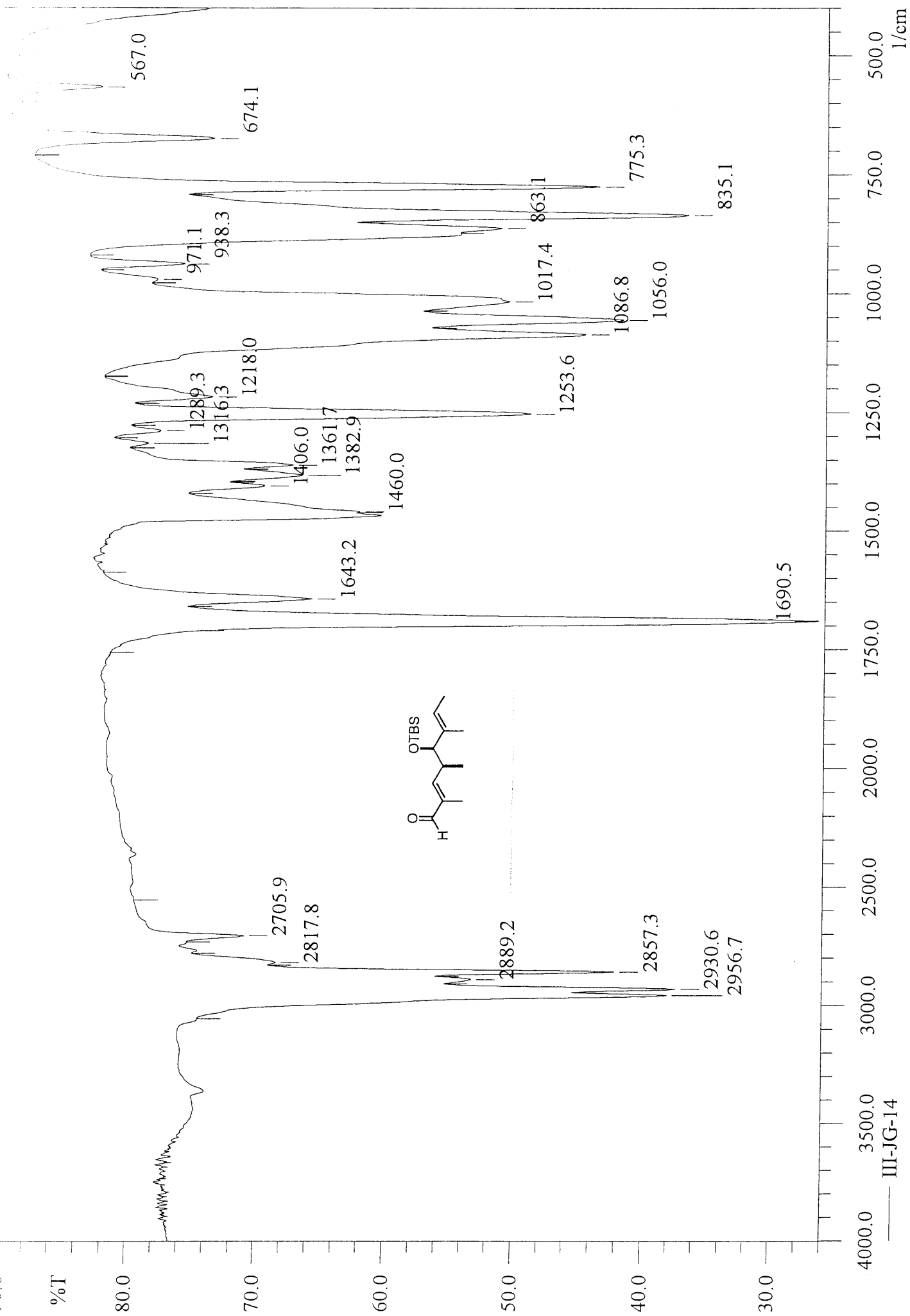


III-JG-14  
COSY  
CDCl<sub>3</sub>

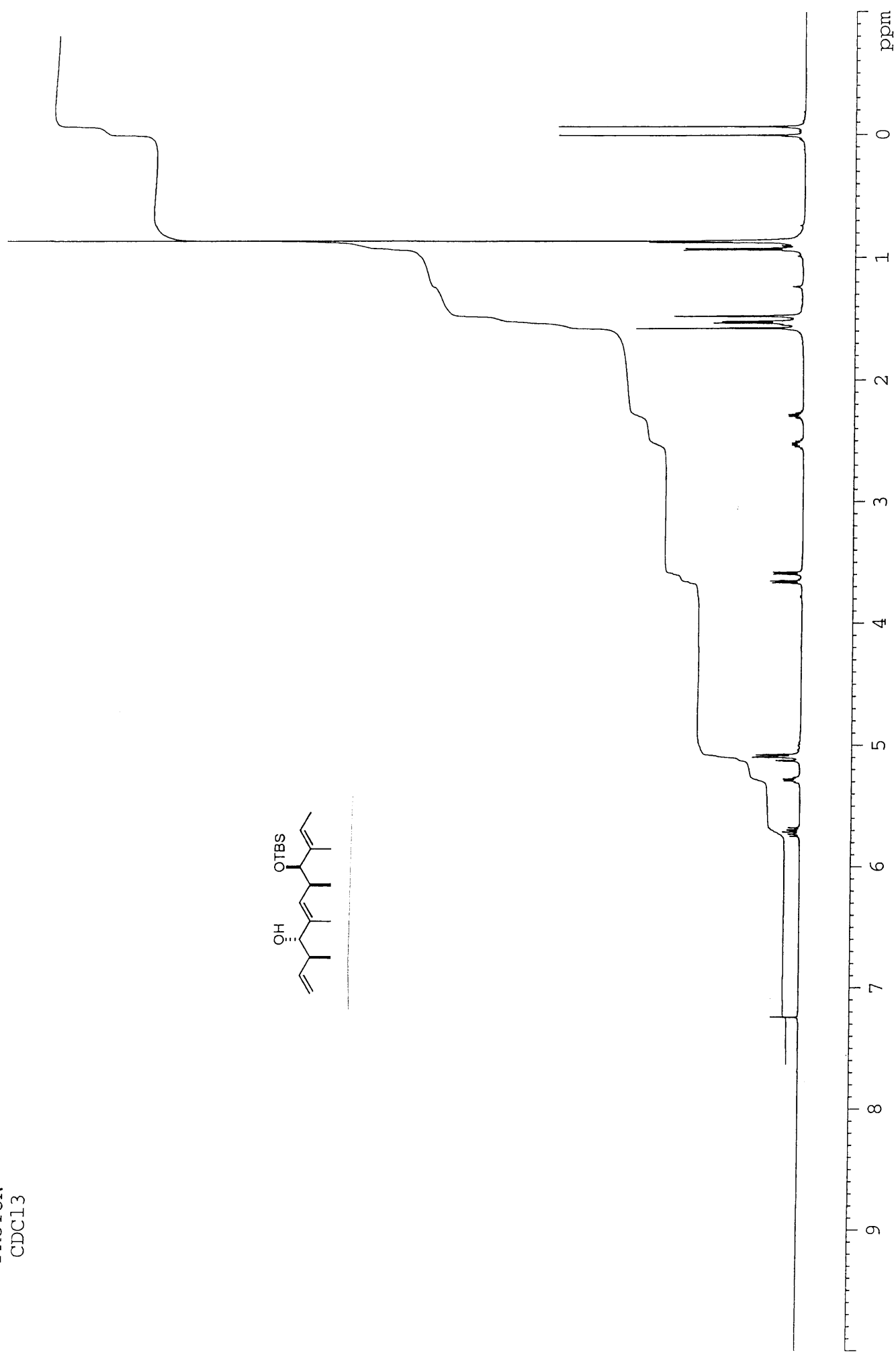
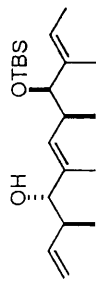


III-JG-14  
HMQC  
CDCl<sub>3</sub>





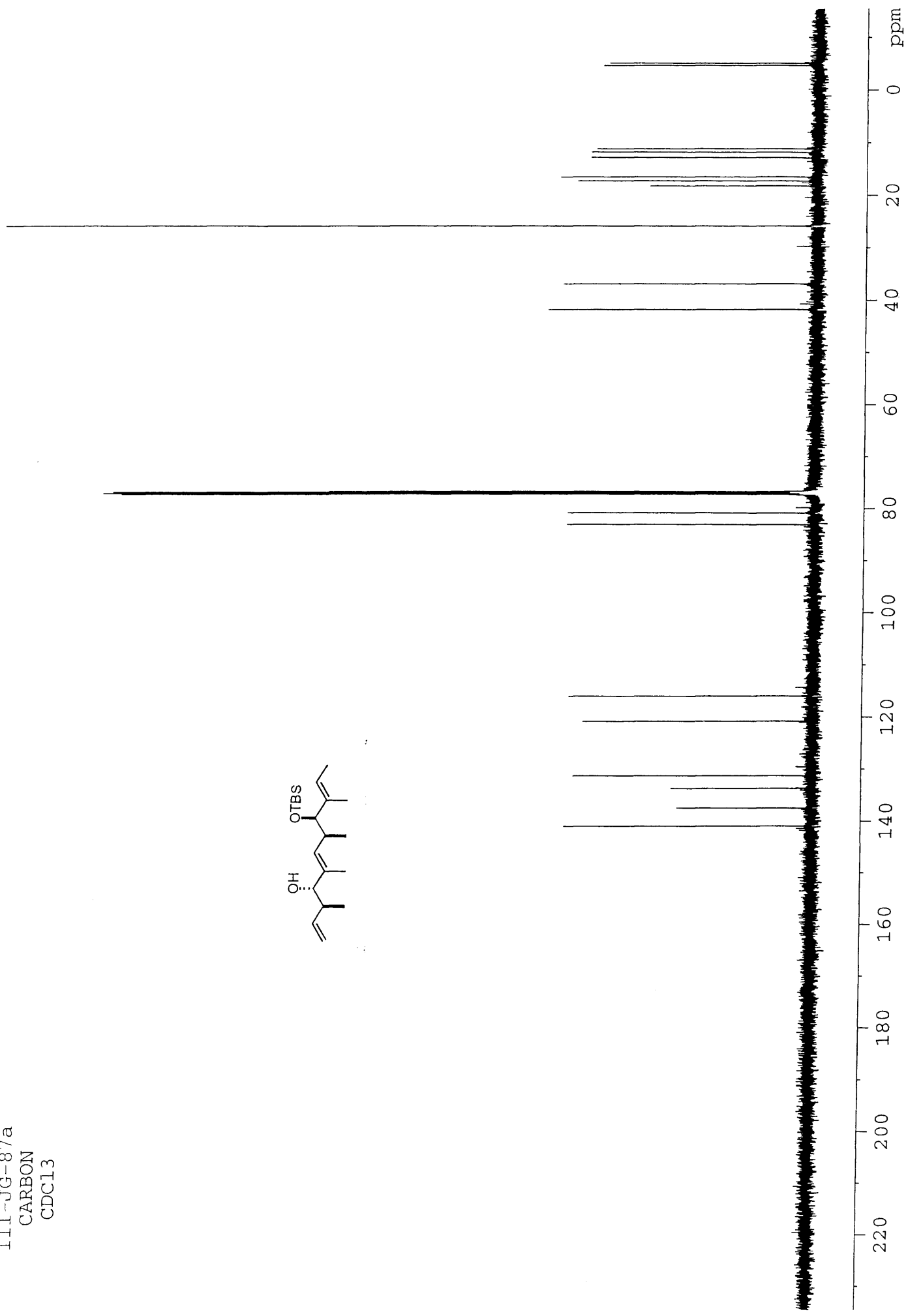
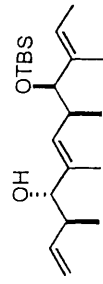
III-JG-87a  
PROTON  
CDCl<sub>3</sub>



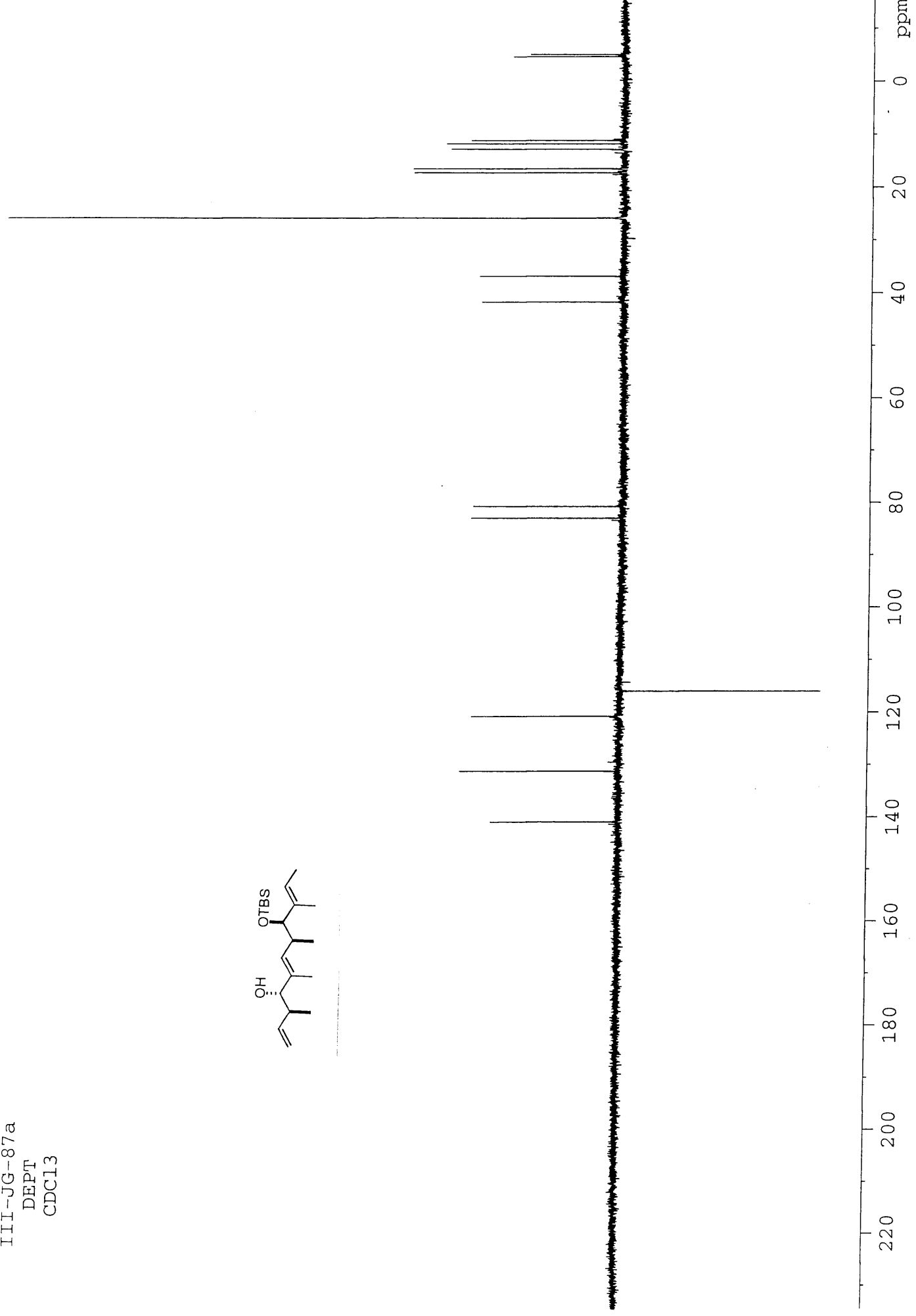
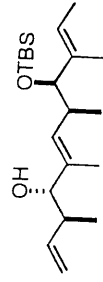
III-JG-87a

# CARBON

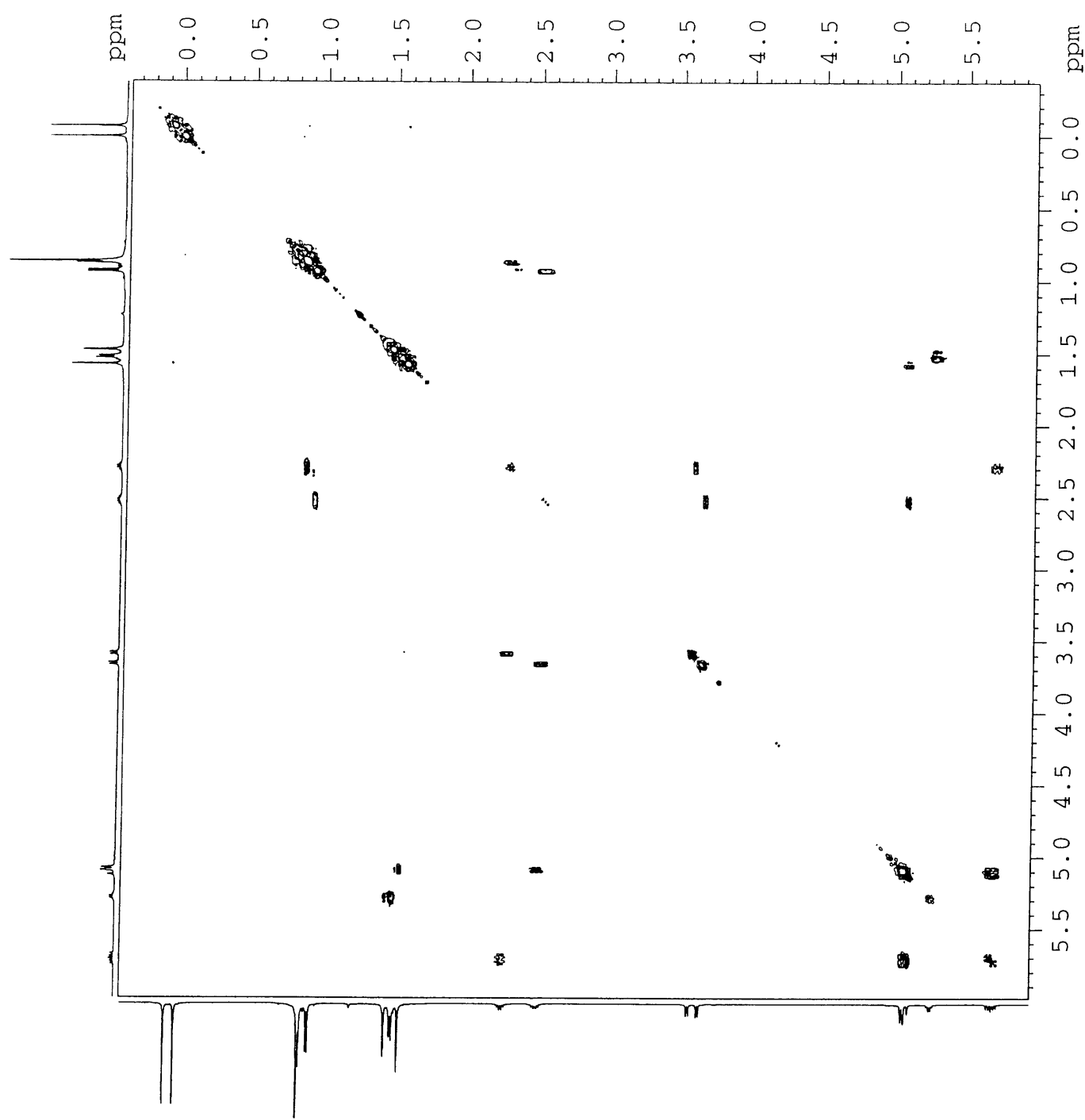
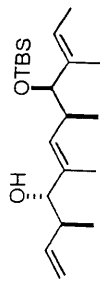
CDC13



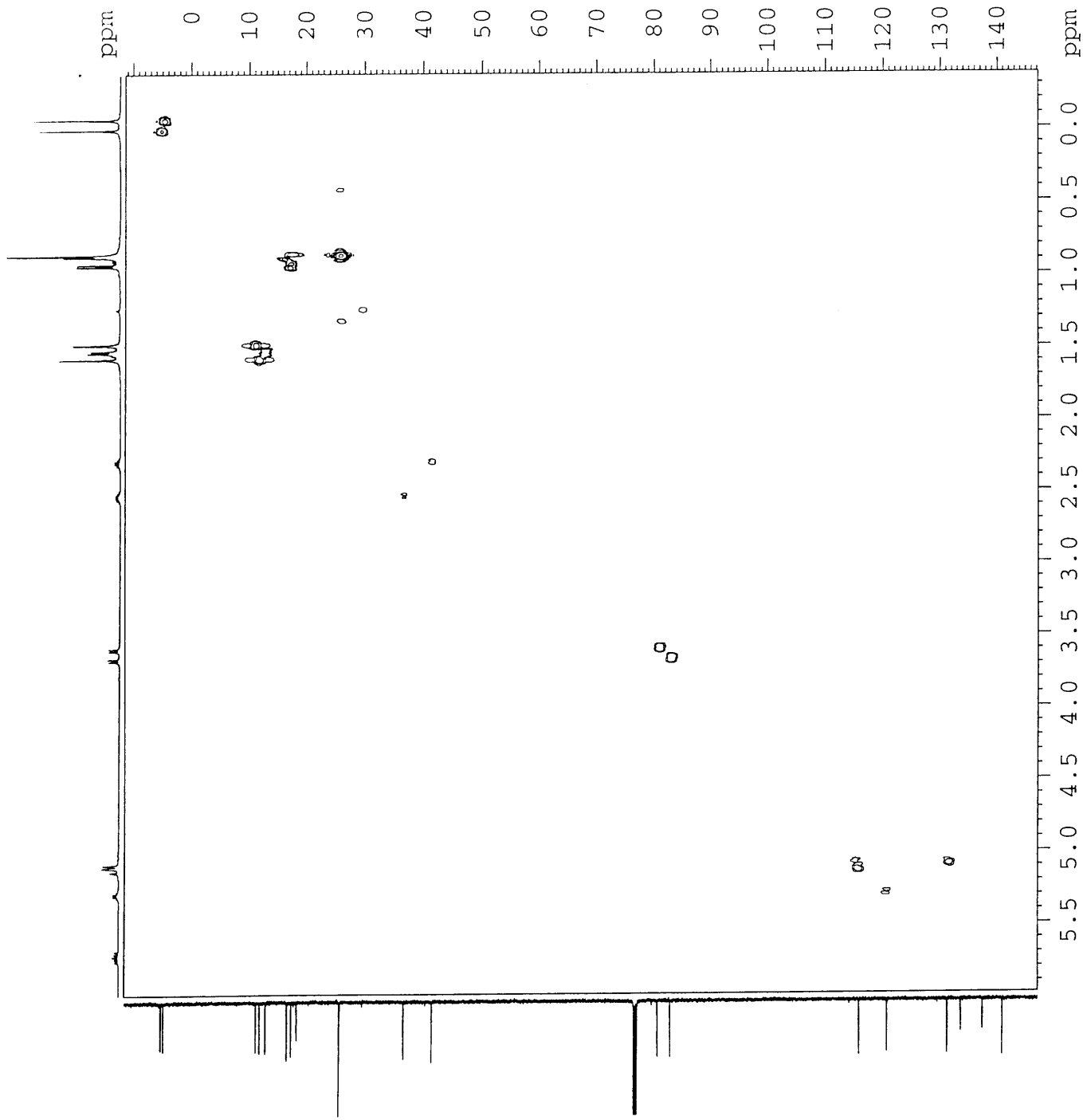
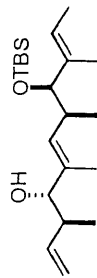
III-JG-87a  
DEPT  
CDCl<sub>3</sub>



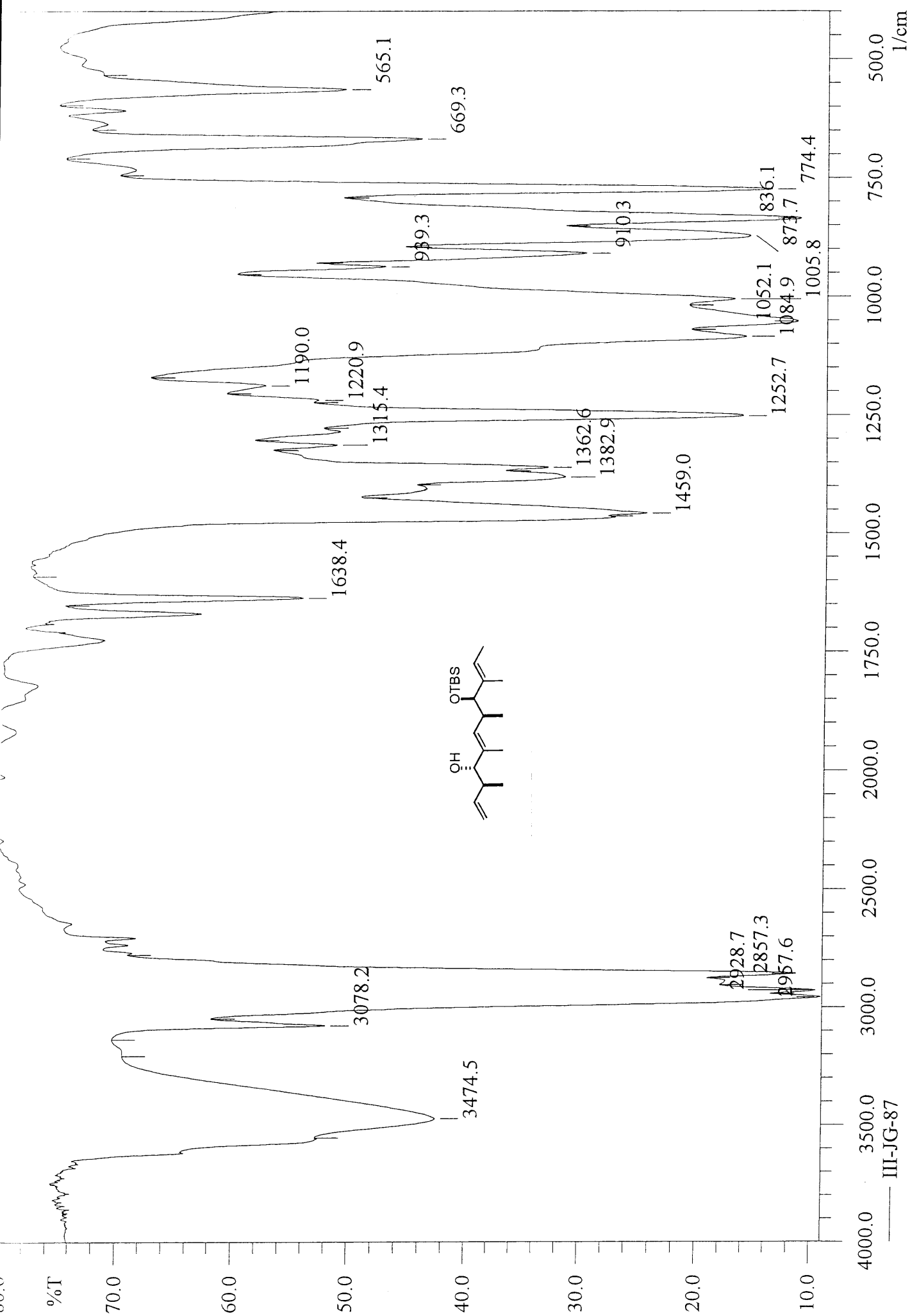
CDC13



III-JG-87a  
HMQC  
CDCl<sub>3</sub>



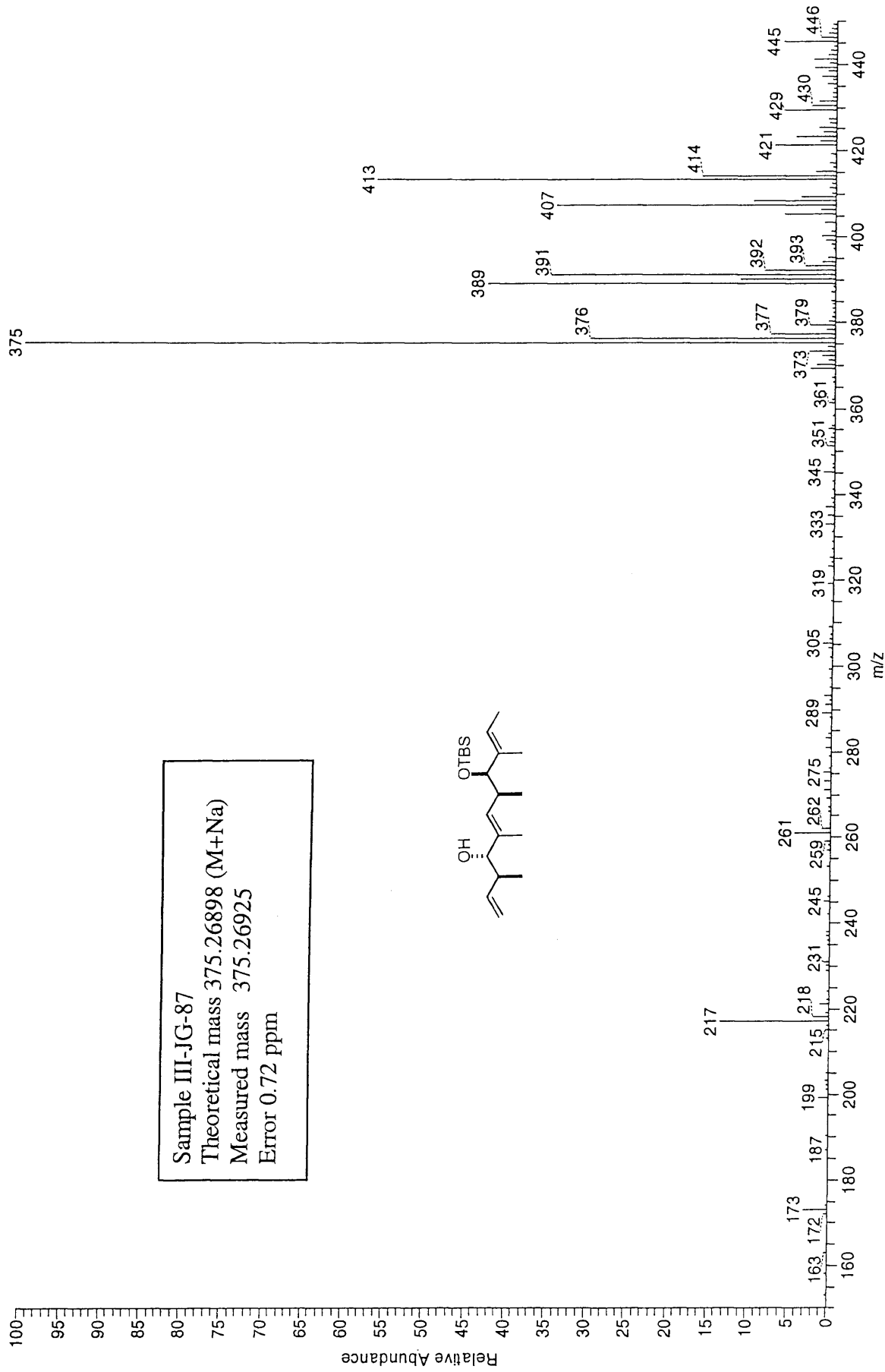
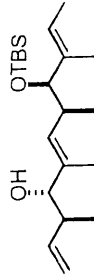




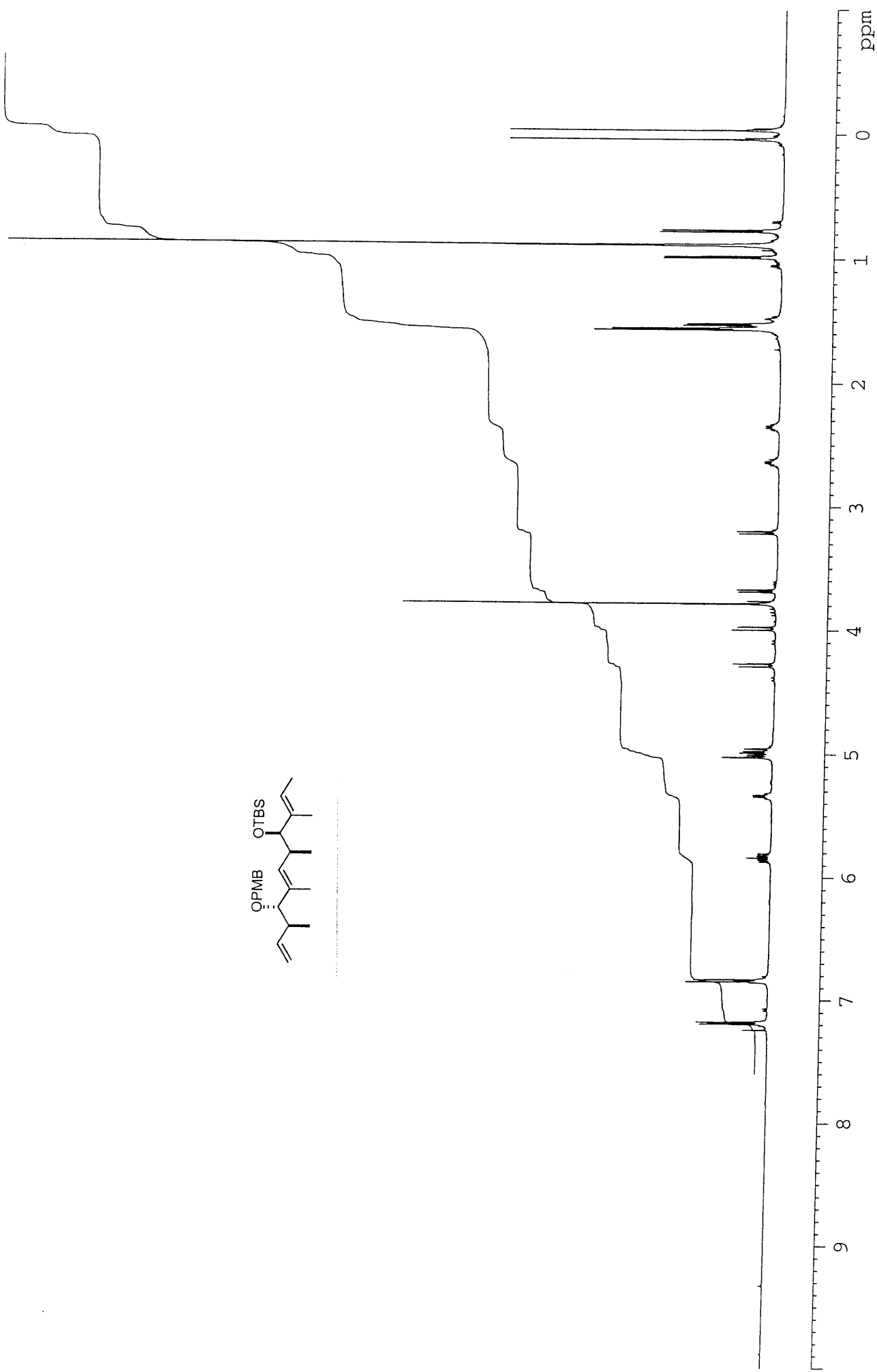
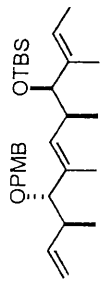
III-JG-87

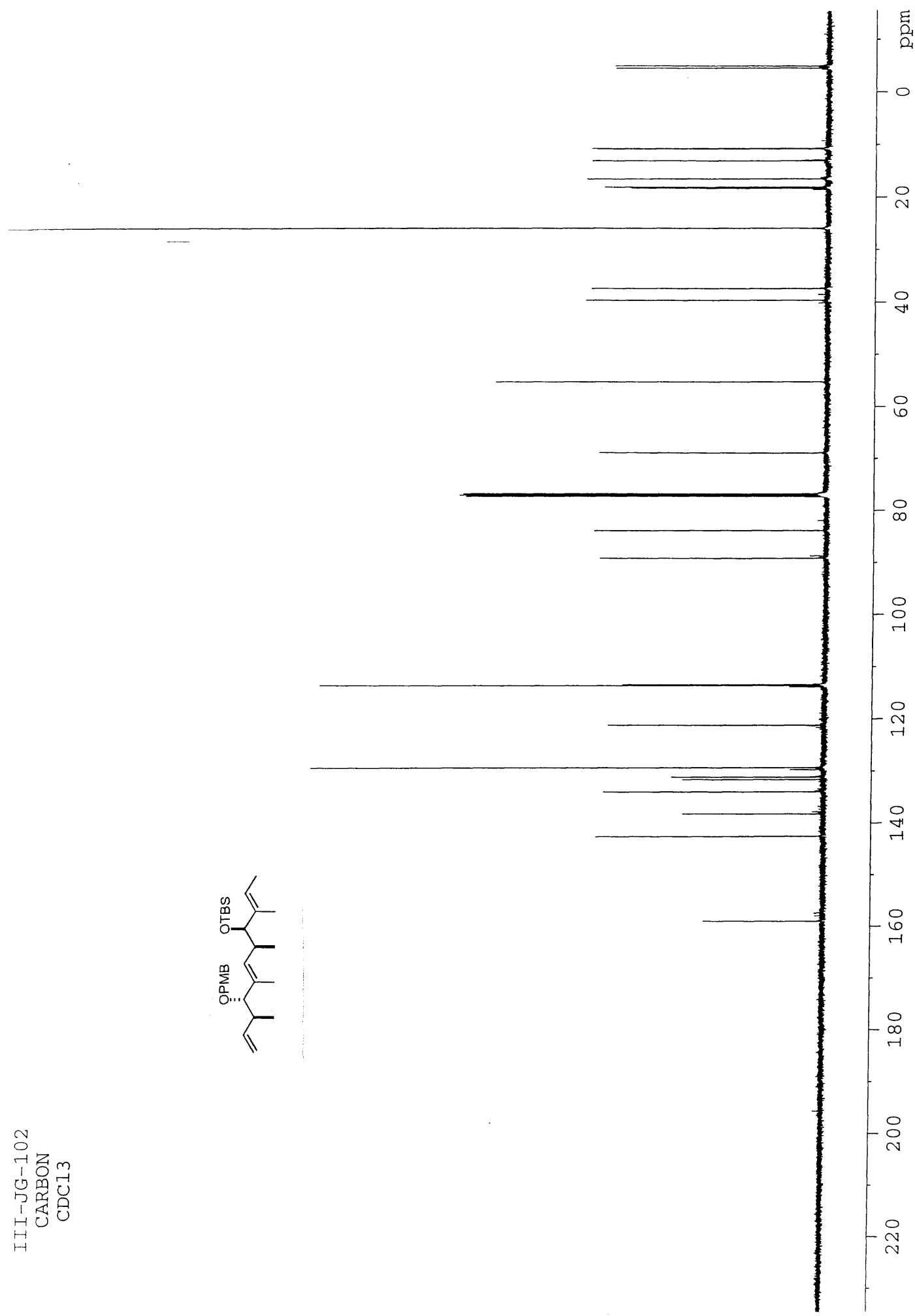
jg87 #40-47 RT: 1.99-2.33 AV:  
T: + c ESI Full ms [99.50-800.50]

Sample III-JG-87  
Theoretical mass 375.26898 (M+Na)  
Measured mass 375.26925  
Error 0.72 ppm

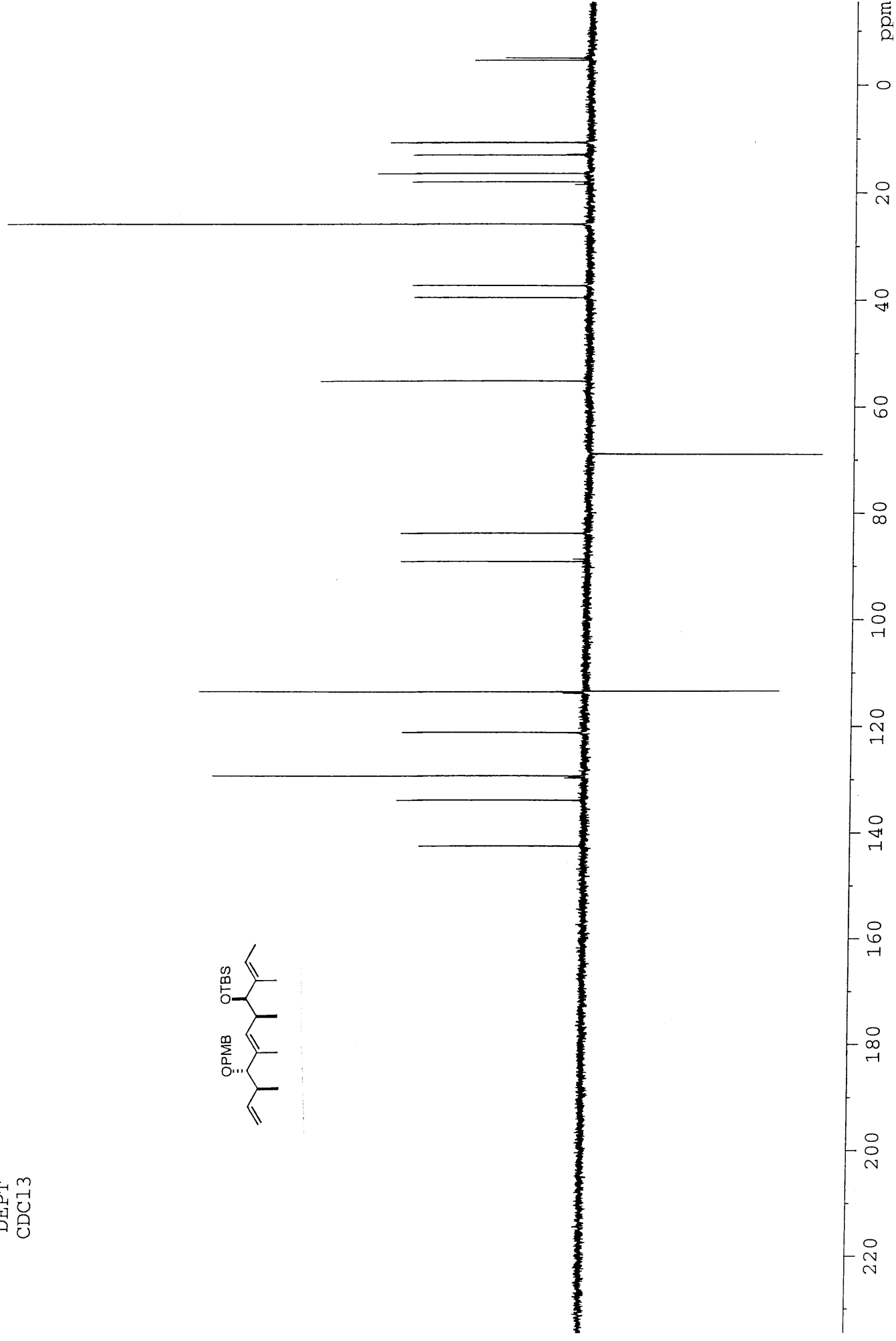


III-JG-102  
PROTON  
CDC13

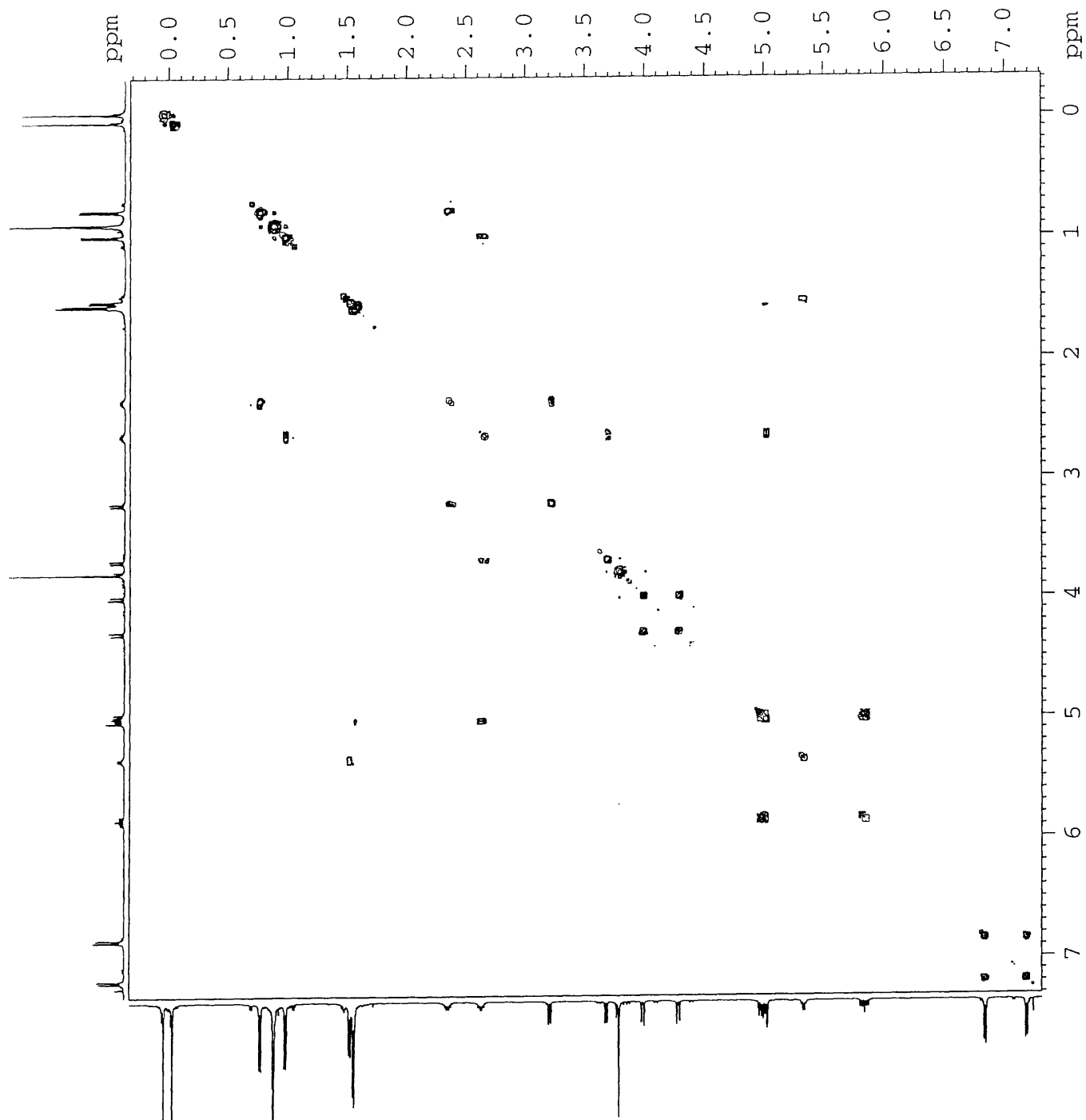
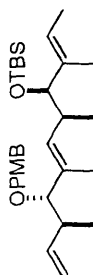


C=C[C@H](C=C)[C@H](C=C)[C@H](C=C)C=C

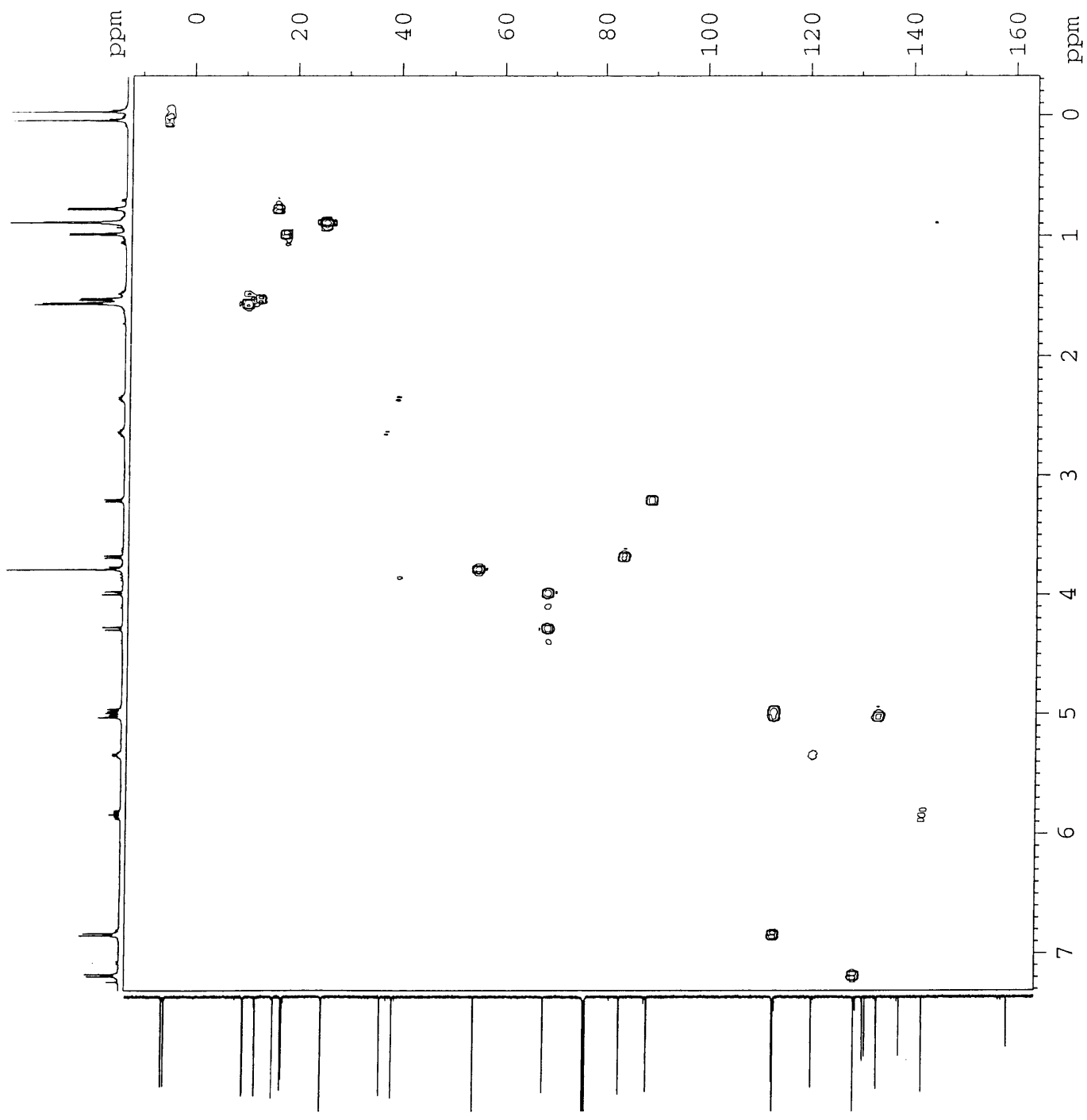
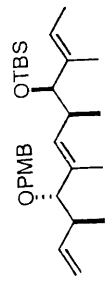
CDC13

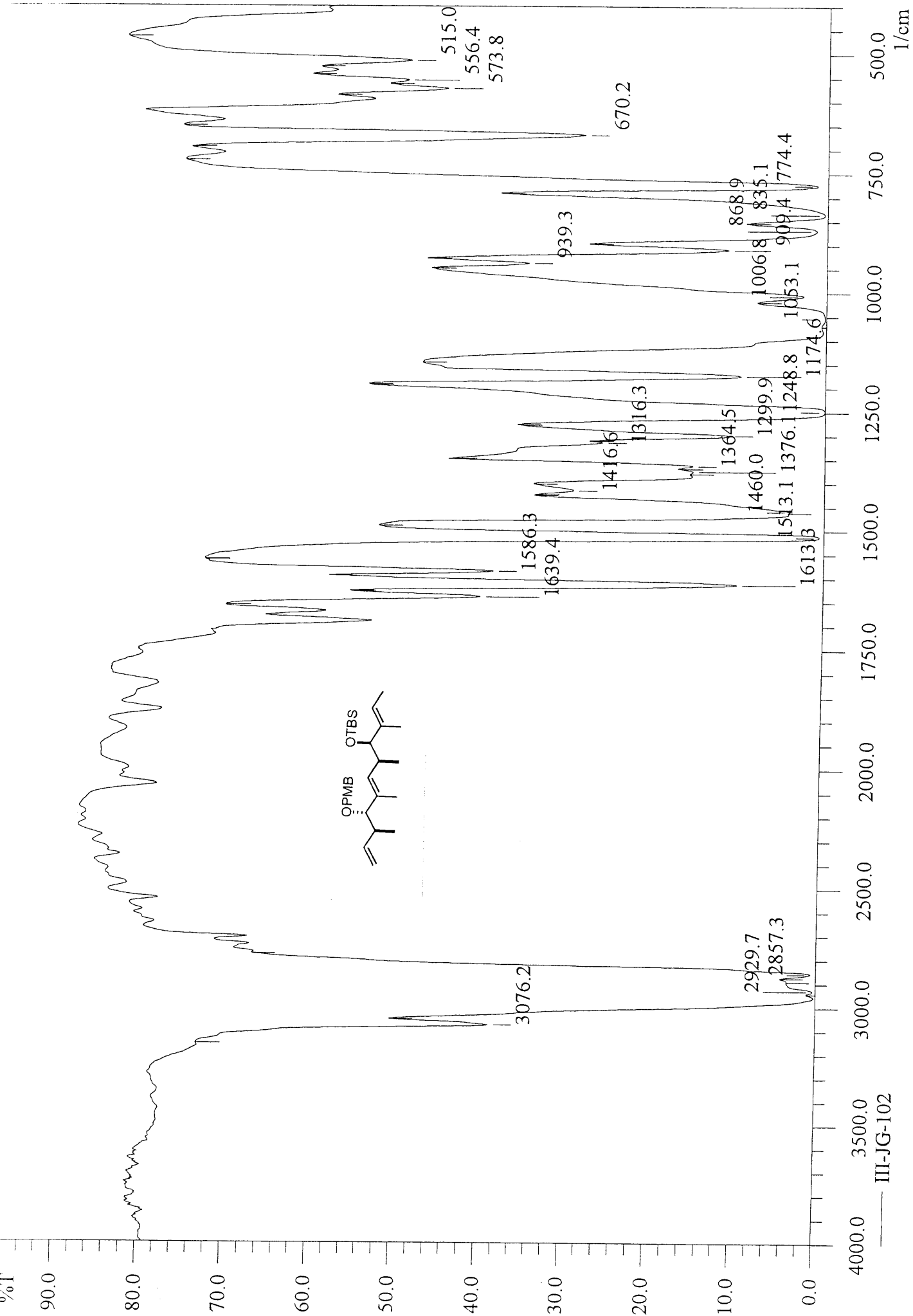


CDC13



CDC13





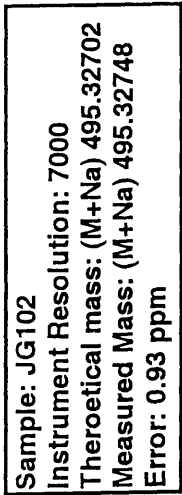


**Sample:** JG102  
**Instrument Resolution:** 7000  
**Theoretical mass: (M+Na)** 495.32702  
**Measured Mass: (M+Na)** 495.32748  
**Error:** 0.93 ppm

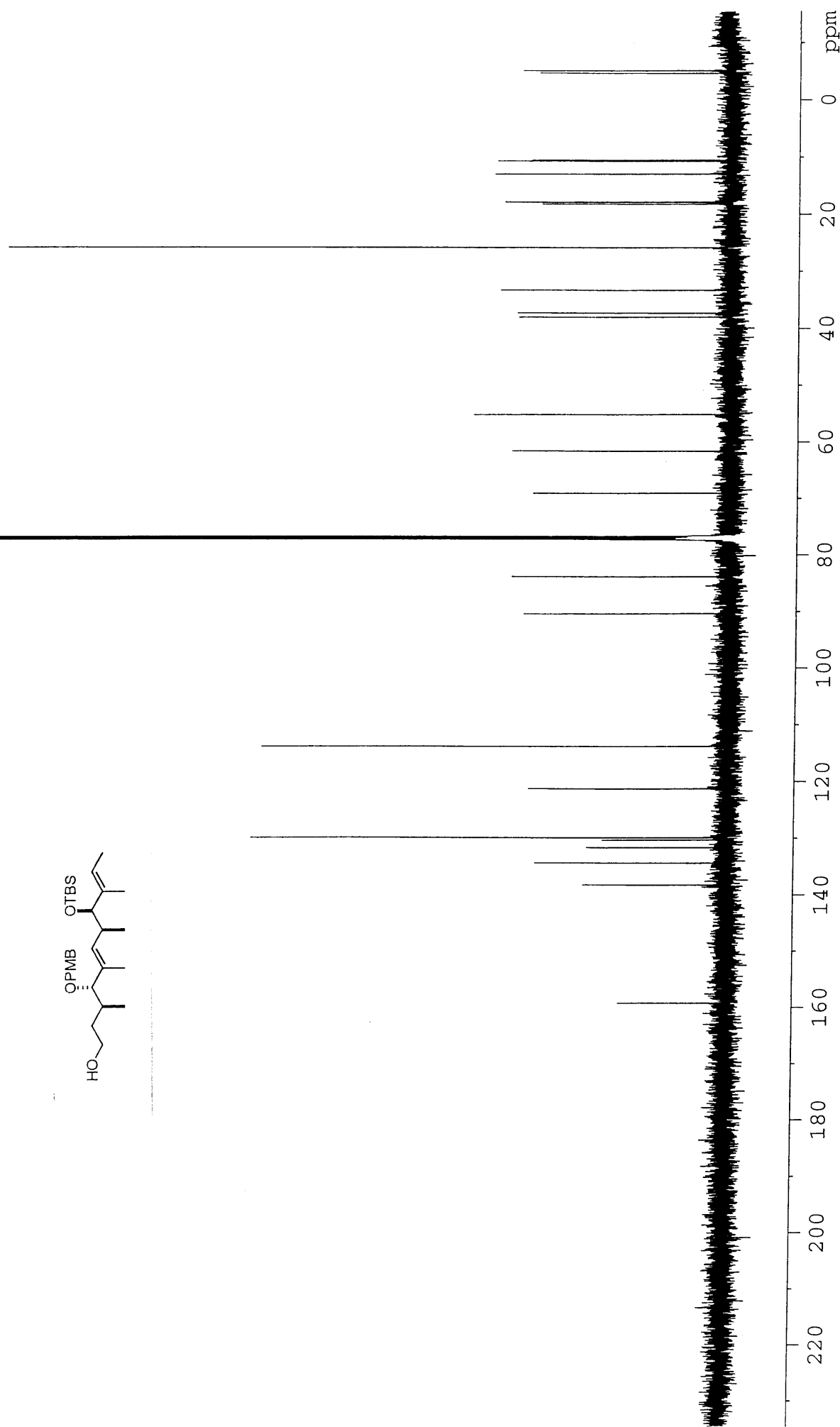
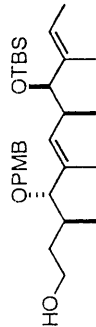
C=C[C@H](C)[C@@H](OC(=O)c1ccc(C)cc1)[C@H](C)/C=C/C(C)=C

OTBS

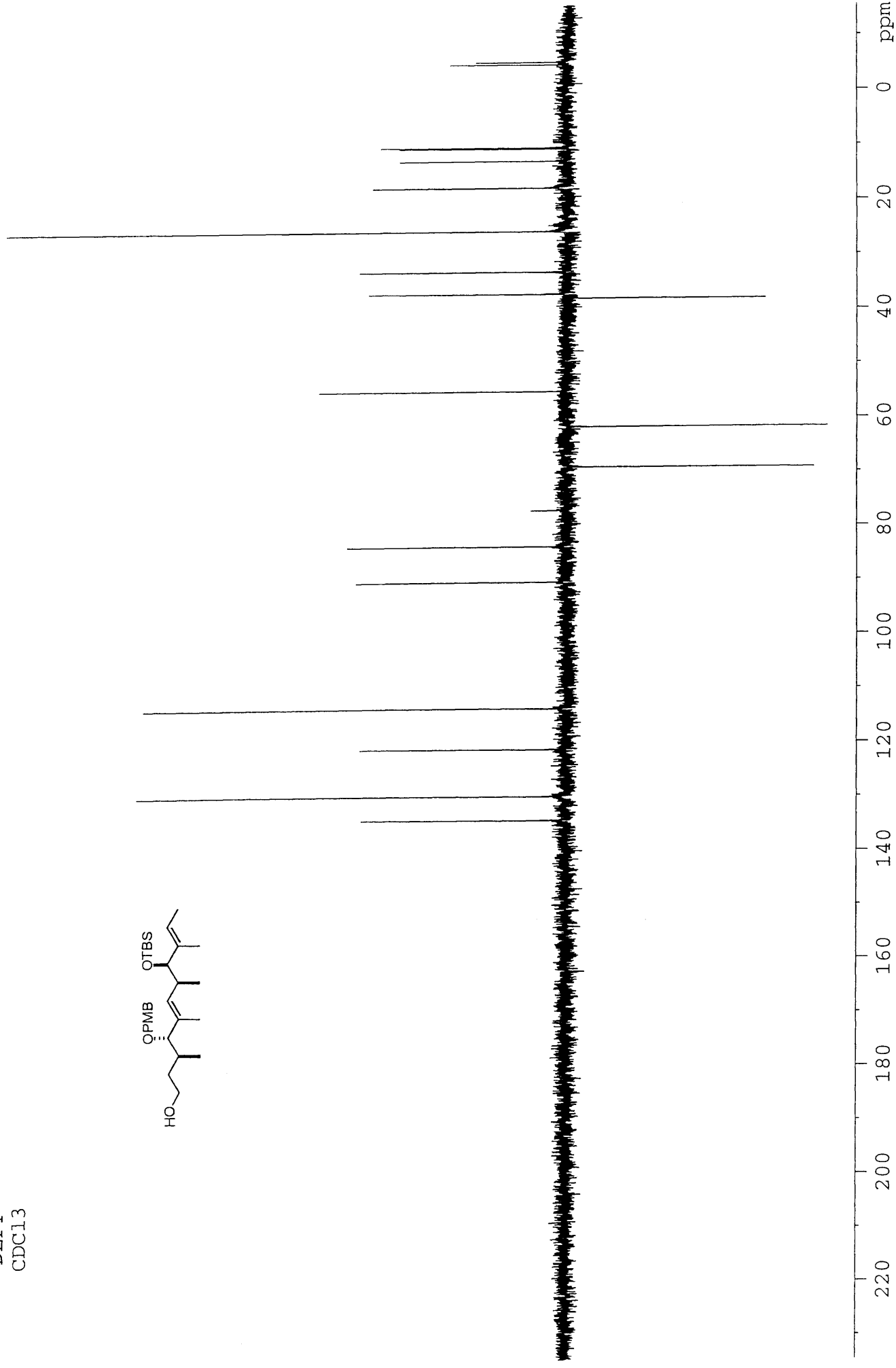
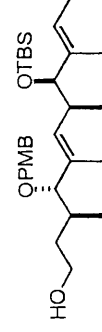
m/z	Relative Intensity (%)
143	~8
173	~12
199	100
279	~5
321	~2
433	~2
495	~10
645	~1

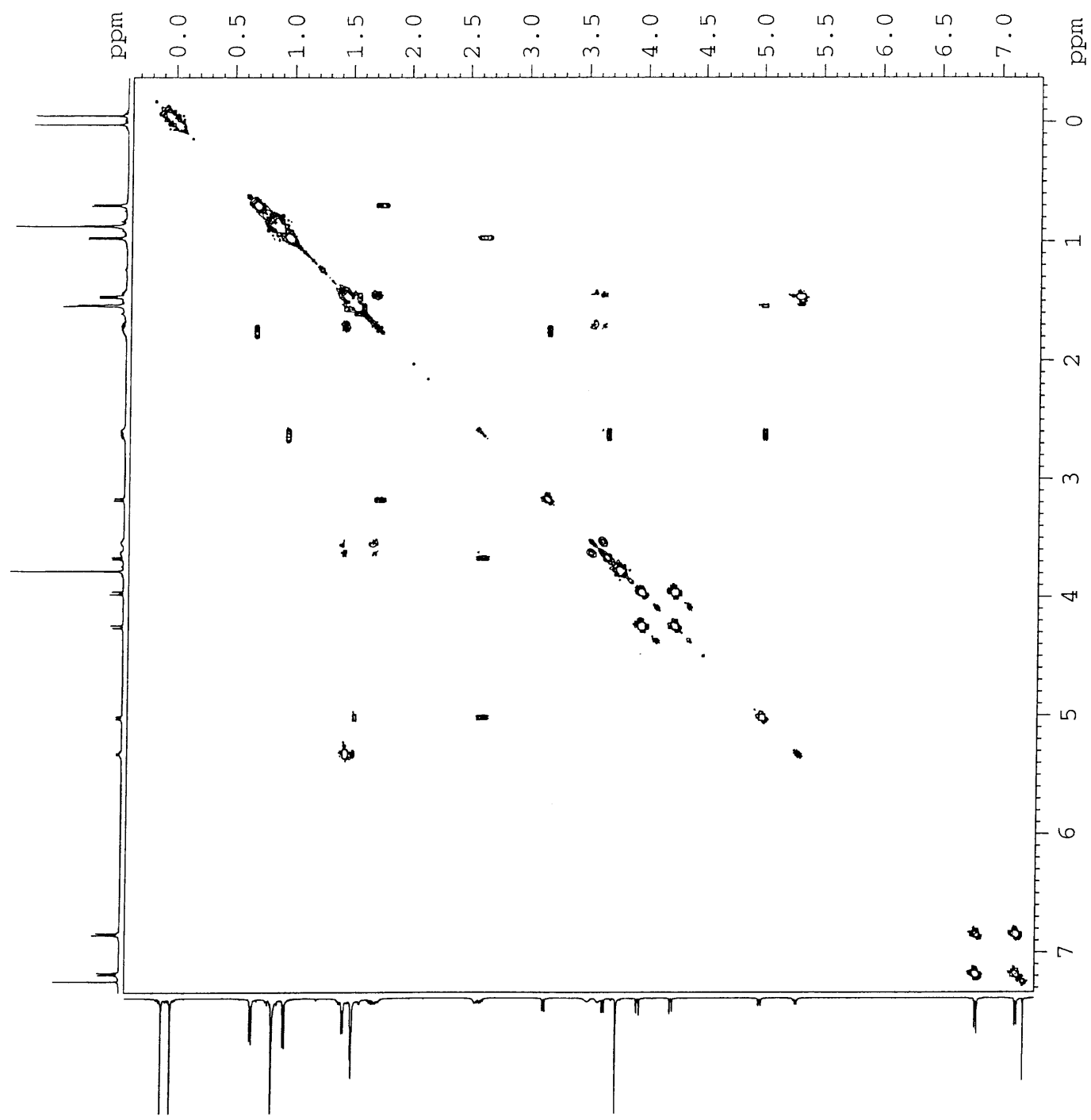


III-JG-164  
CARBON  
CDC13

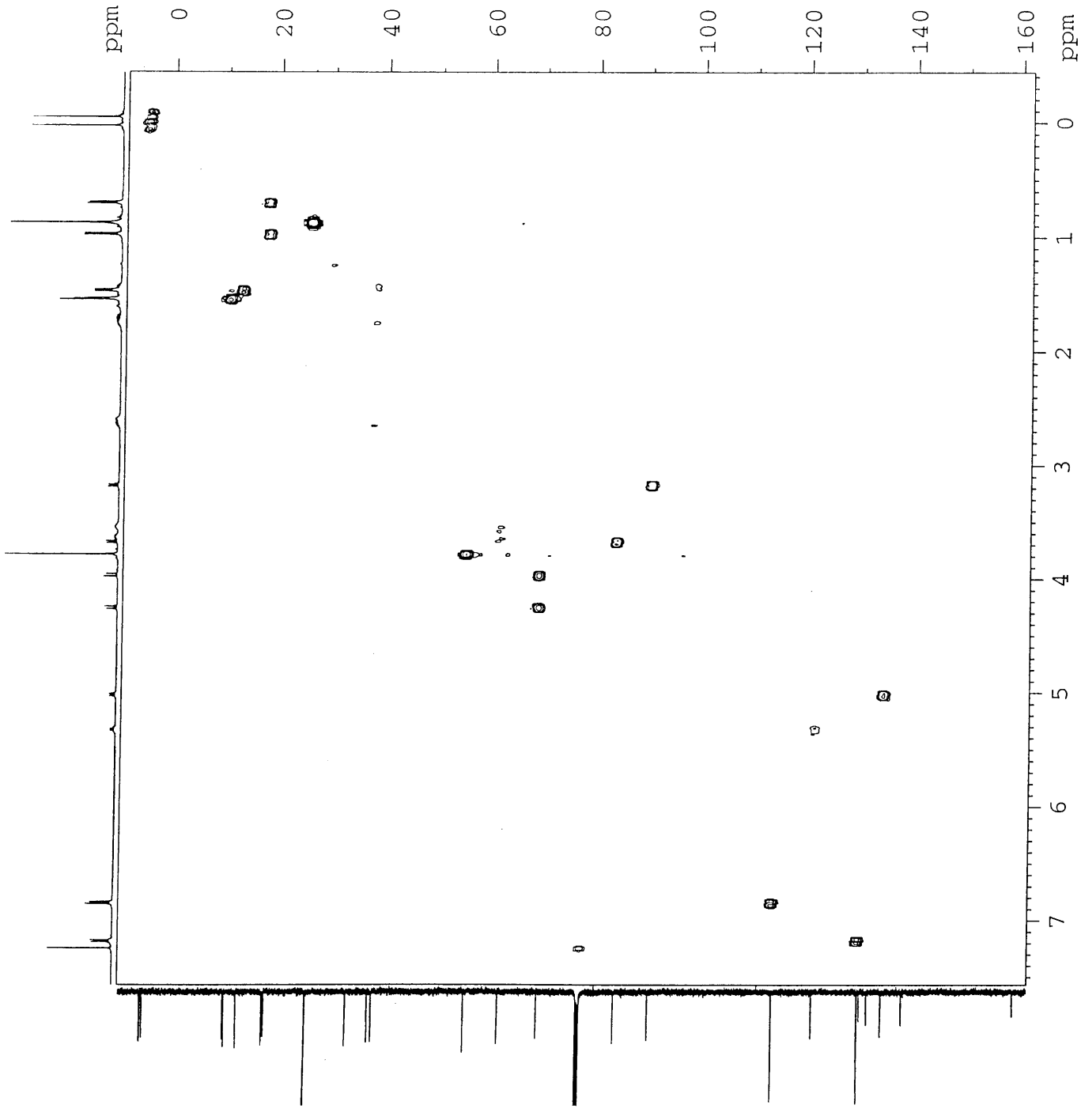
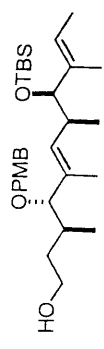


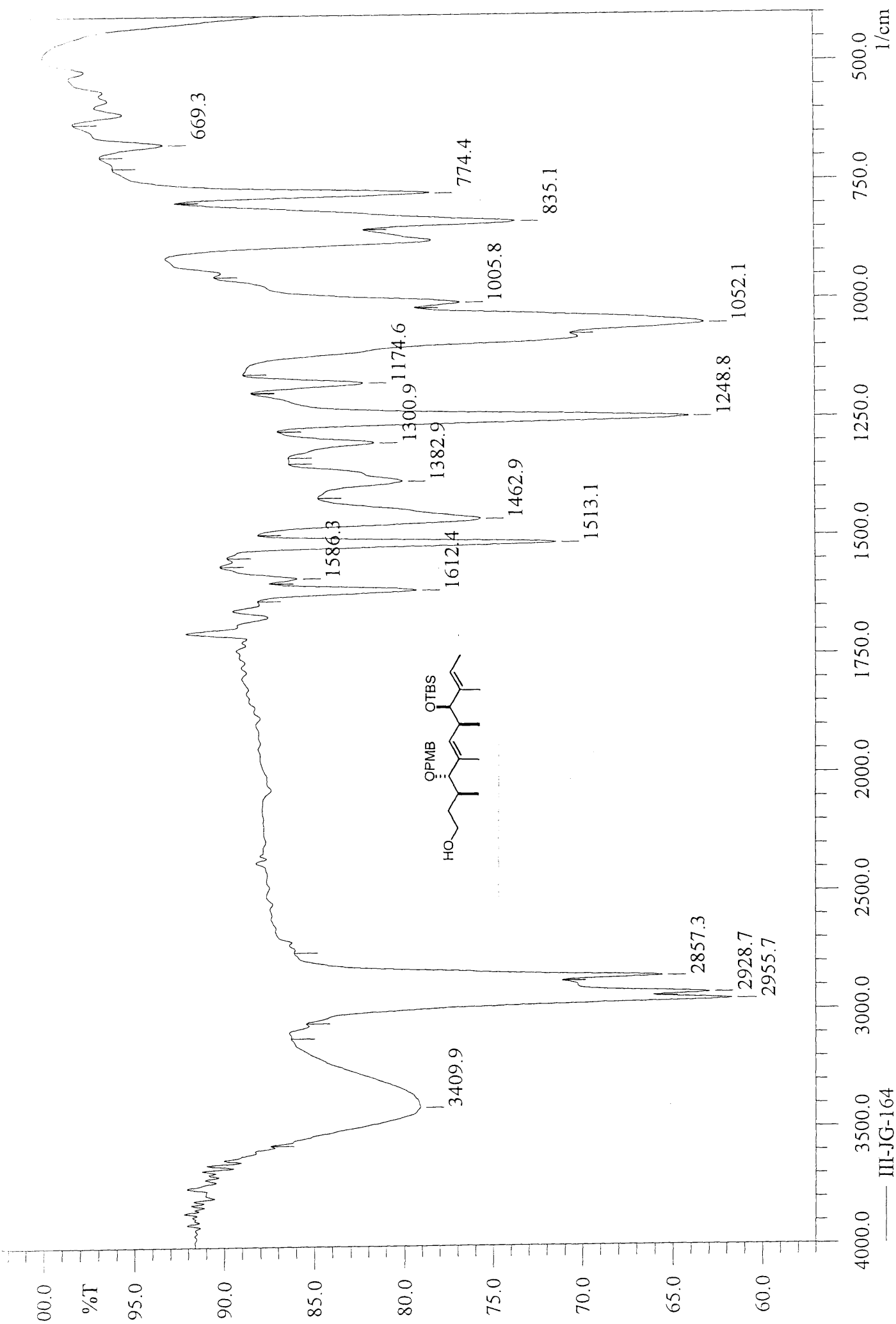
CDC13



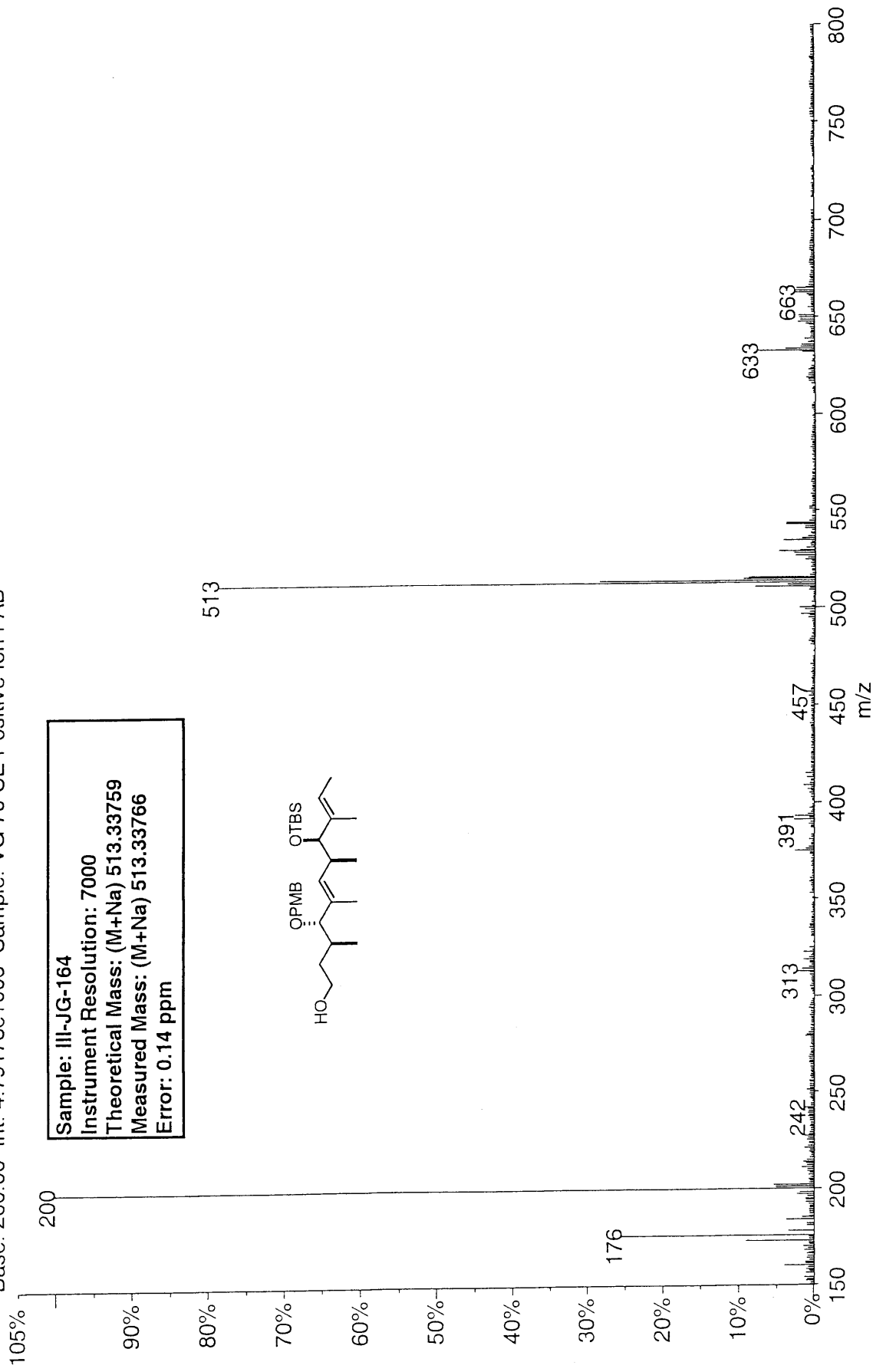
C/C=C/[C@H](OC(=O)c1ccc(C)cc1)[C@@H](OC(=O)c1ccc(C)cc1)[C@H](OC(=O)c1ccc(C)cc1)C

III-JG-164  
HMQC  
CDCl3





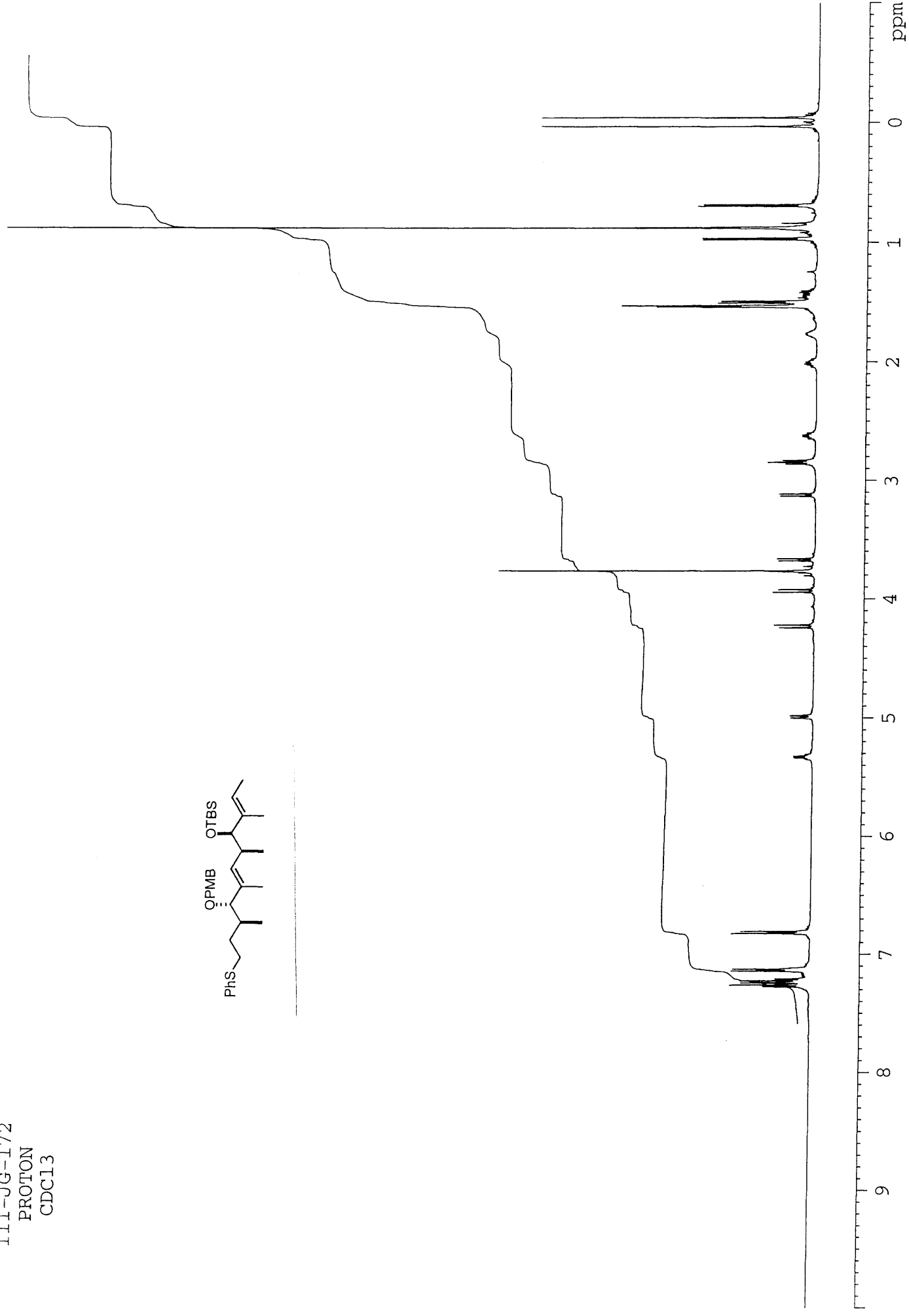
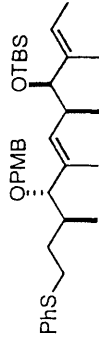
01051005: Scan 213 (39.00 min) - Back  
Base: 200.00 Int: 4.79178e+006 Sample: VG 70-SE Positive Ion FAB



III-JG-172

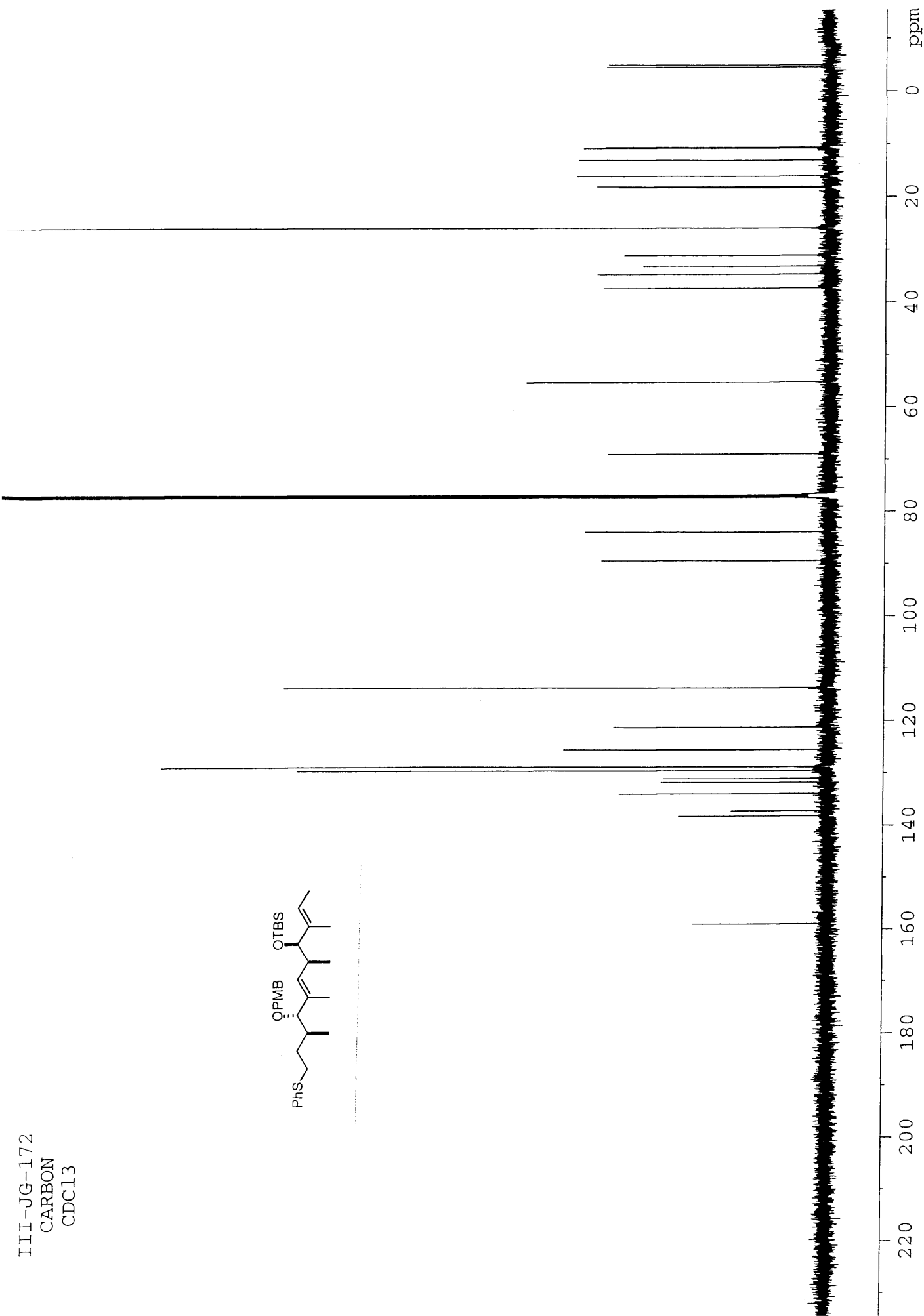
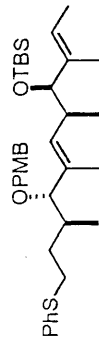
PROTON

CDC13





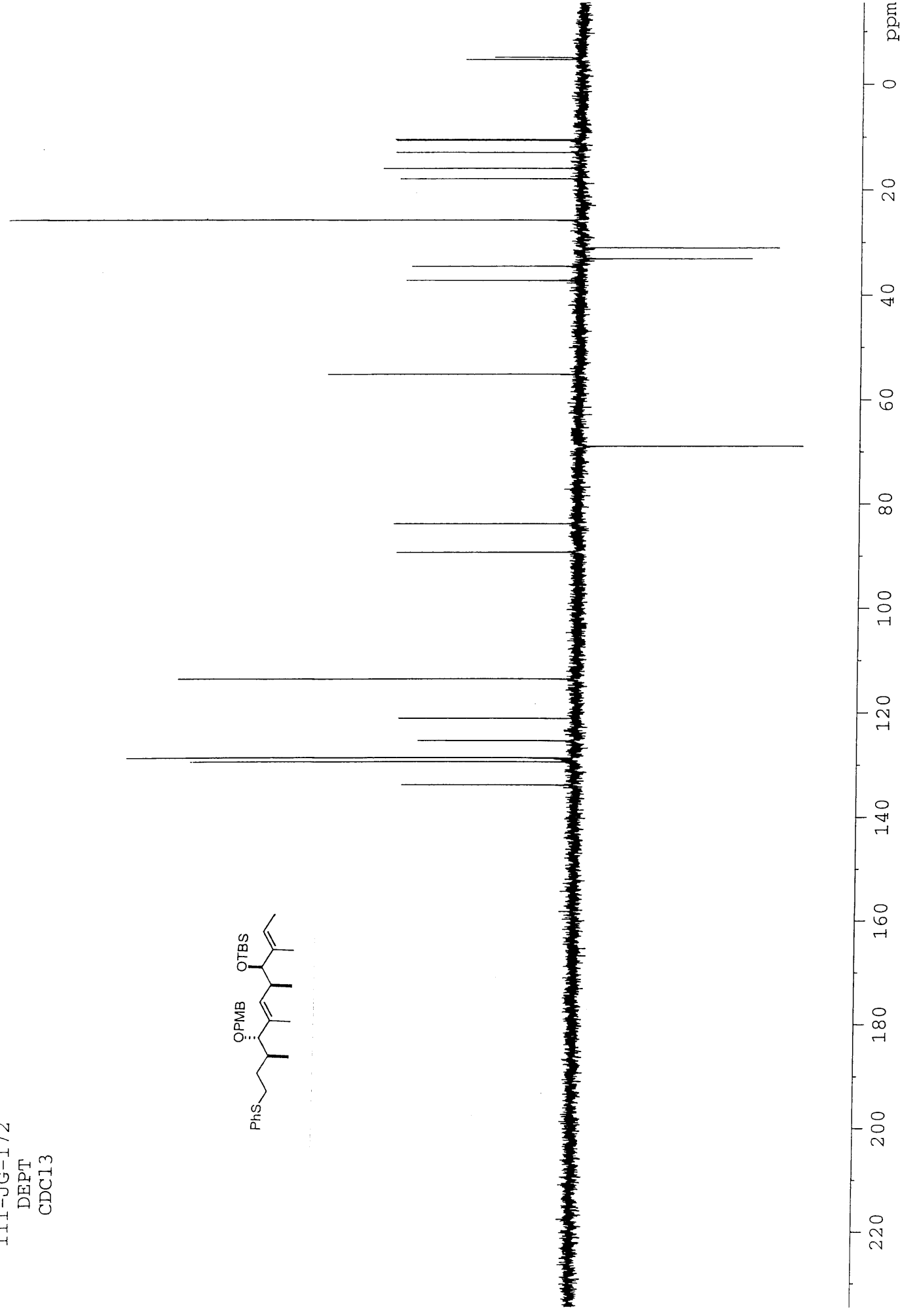
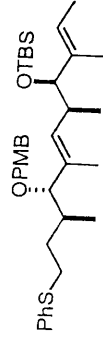
III-JG-172  
CARBON  
CDCl<sub>3</sub>



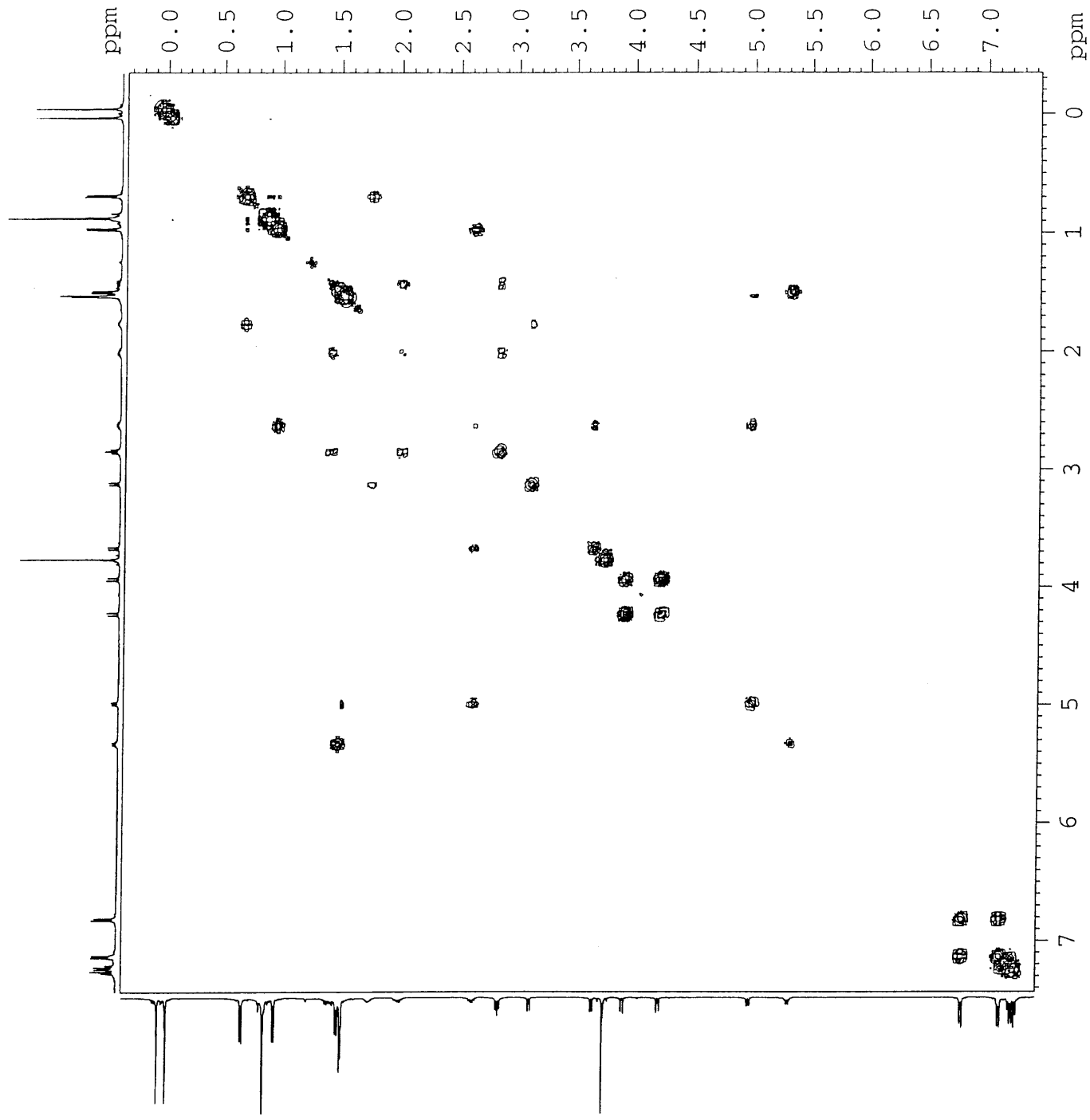
III-JG-172

DEPT

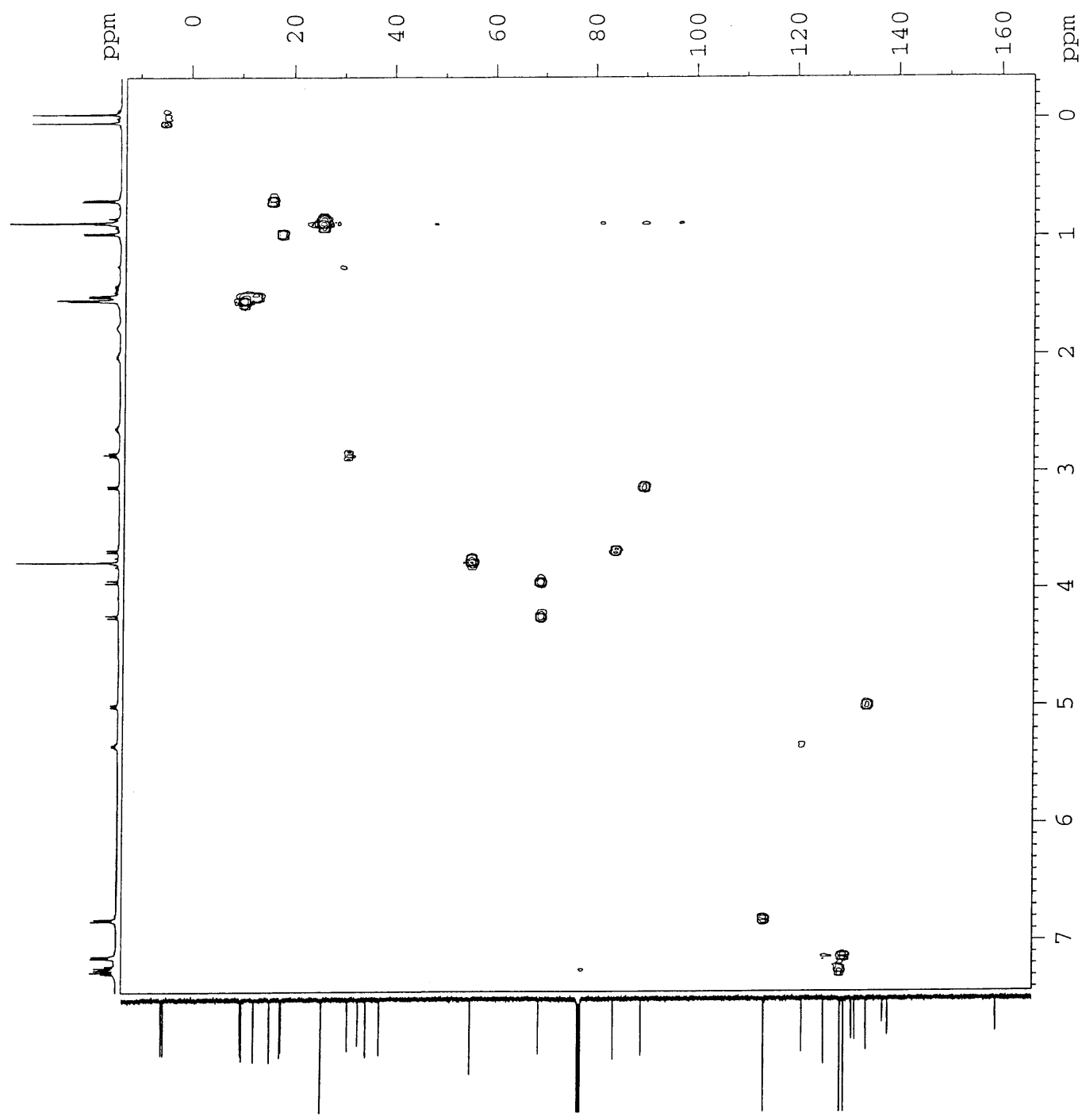
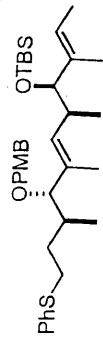
CDCl<sub>3</sub>

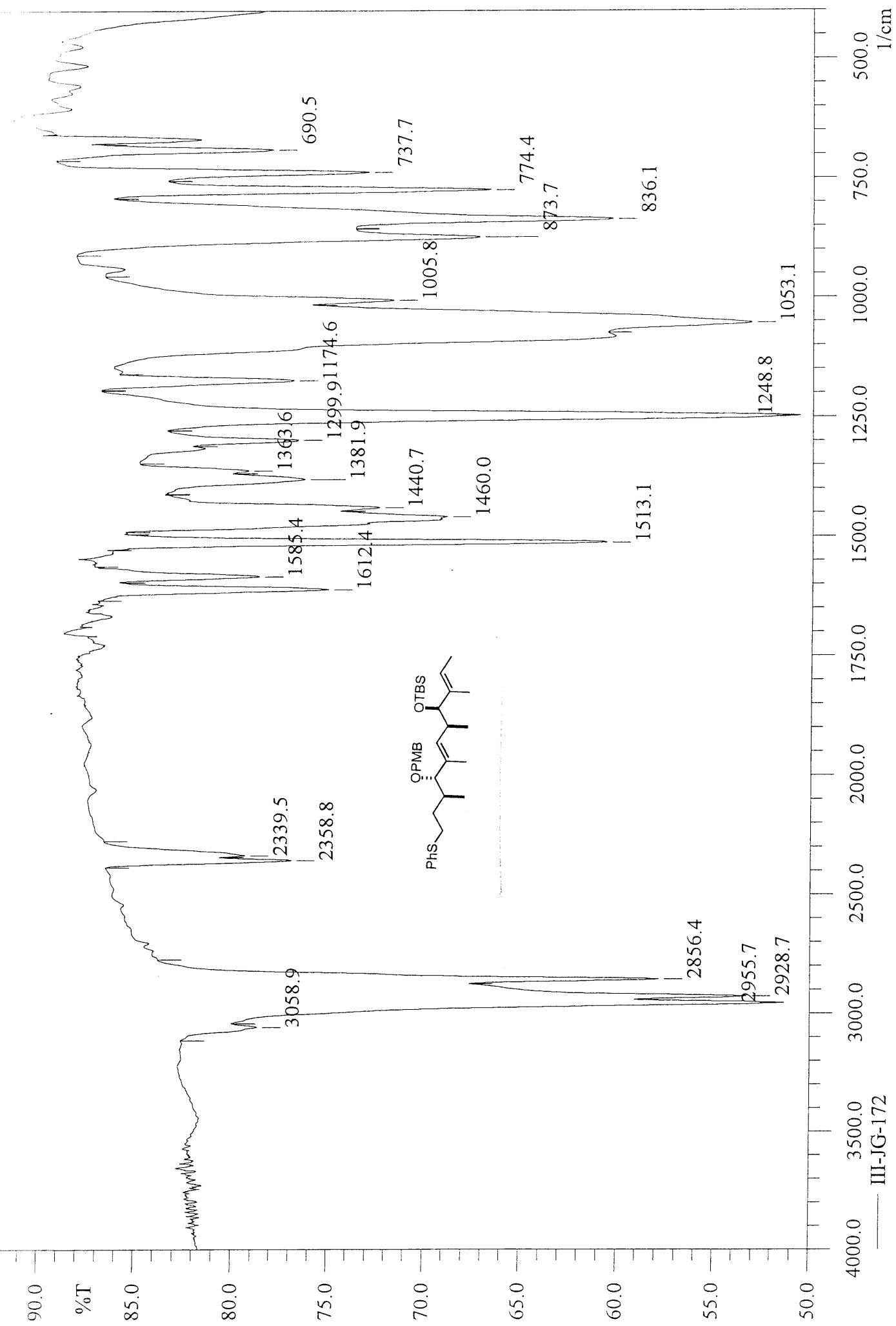


III-JG-172  
COSY  
CDC13

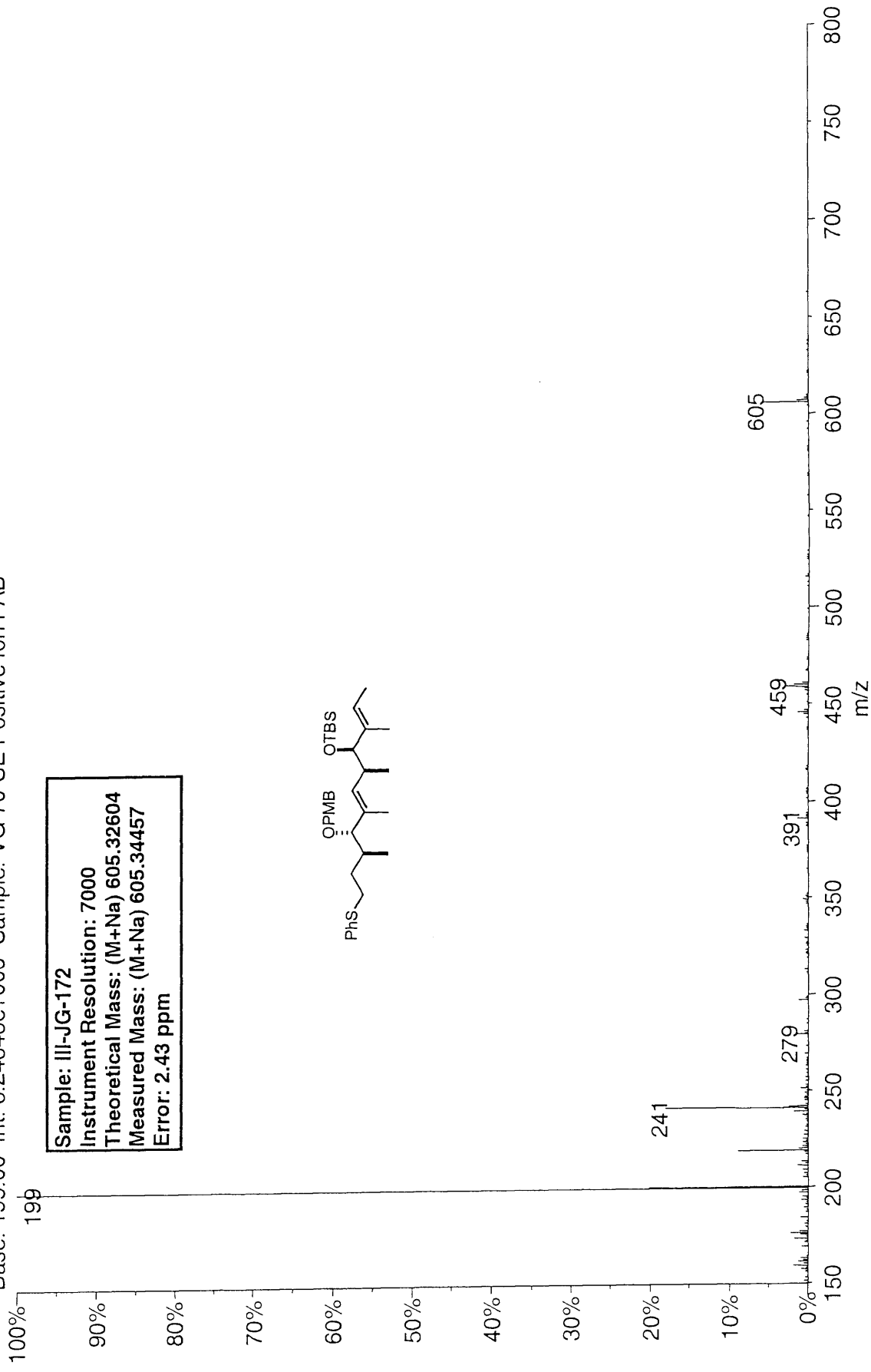


CDC13





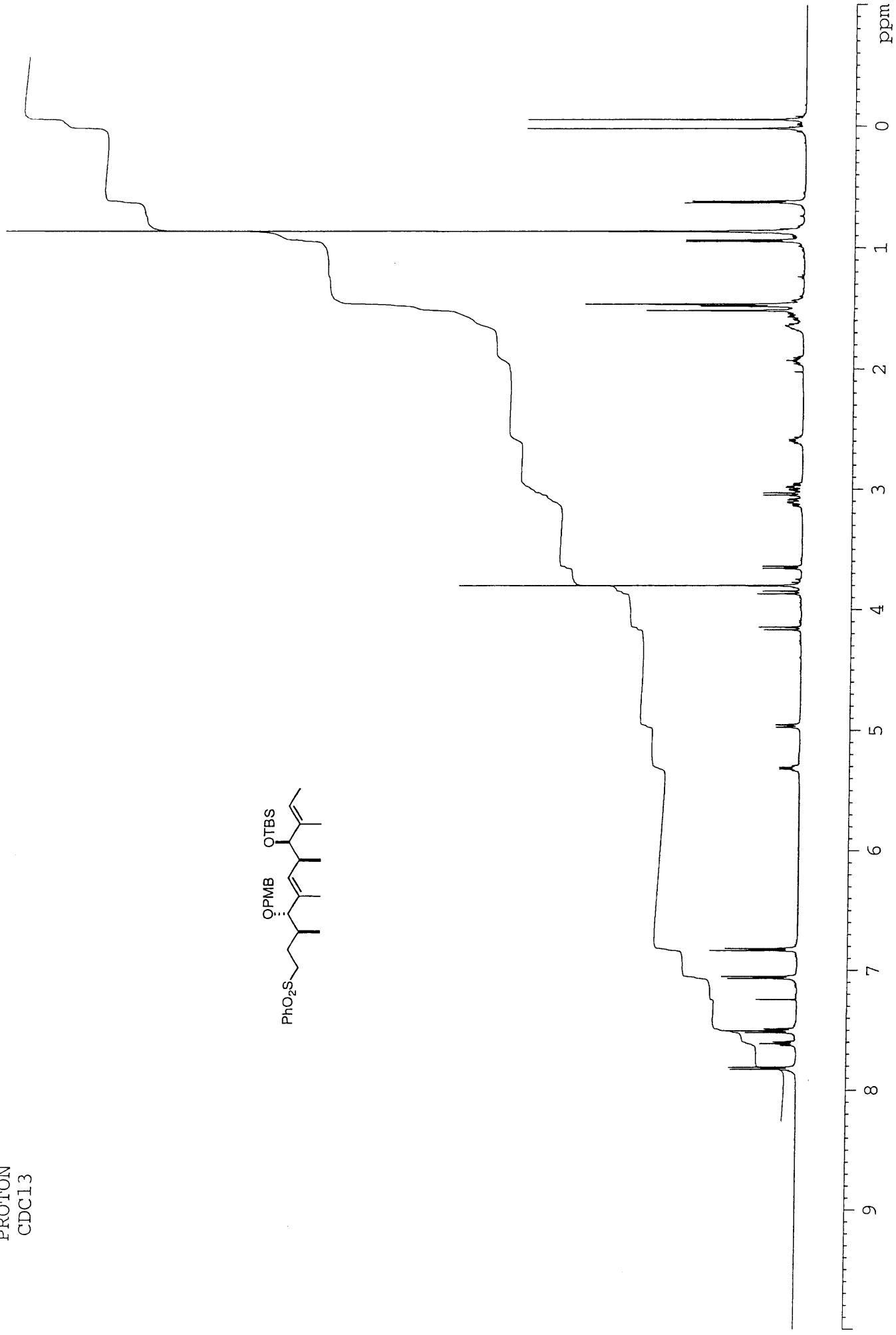
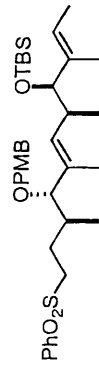
04121005: Scan Avg 102-105 (18.65 - 19.20 min) - Back  
Base: 199.00 Int: 3.24343e+006 Sample: VG 70-SE Positive Ion FAB

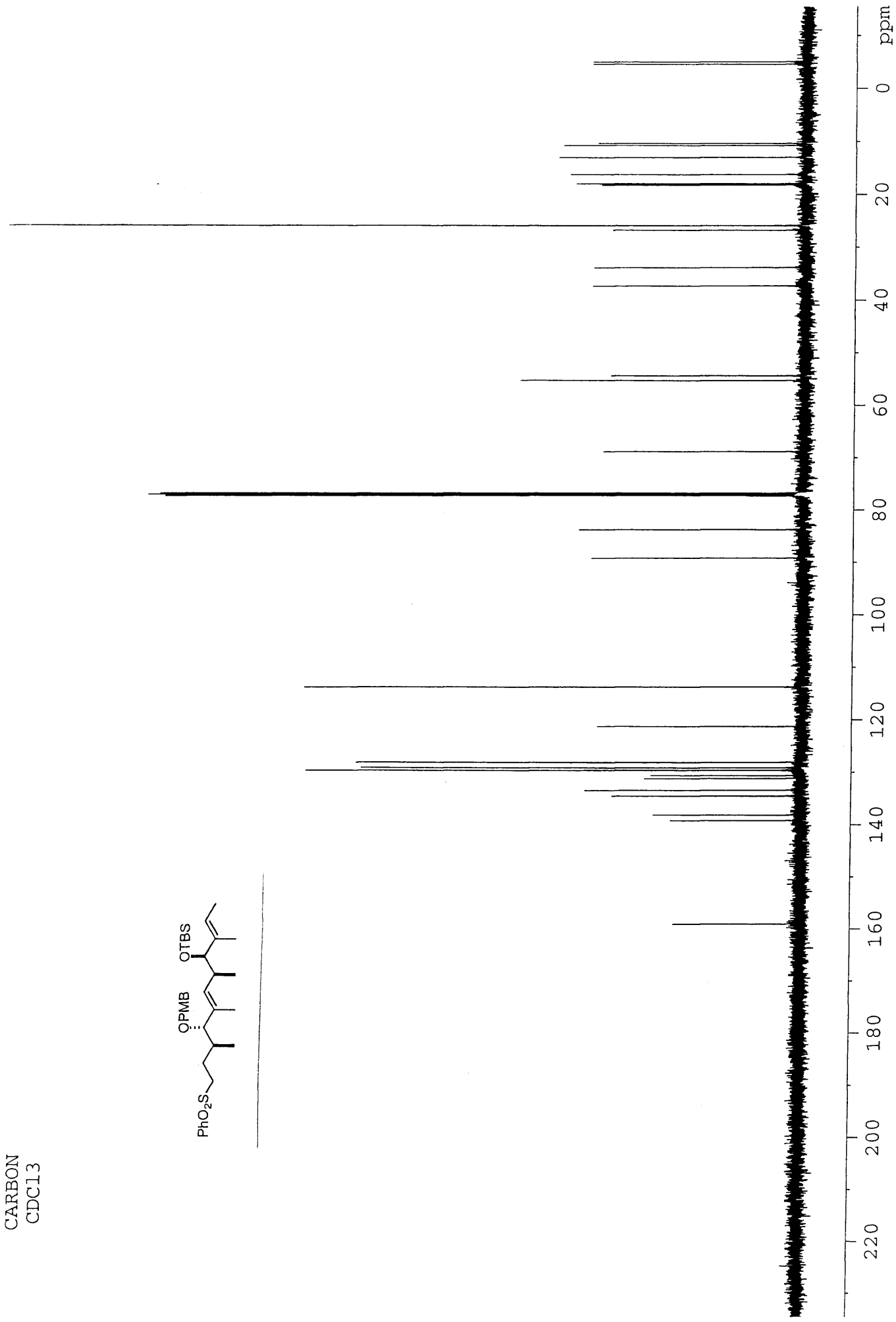


III-JG-173

PROTON

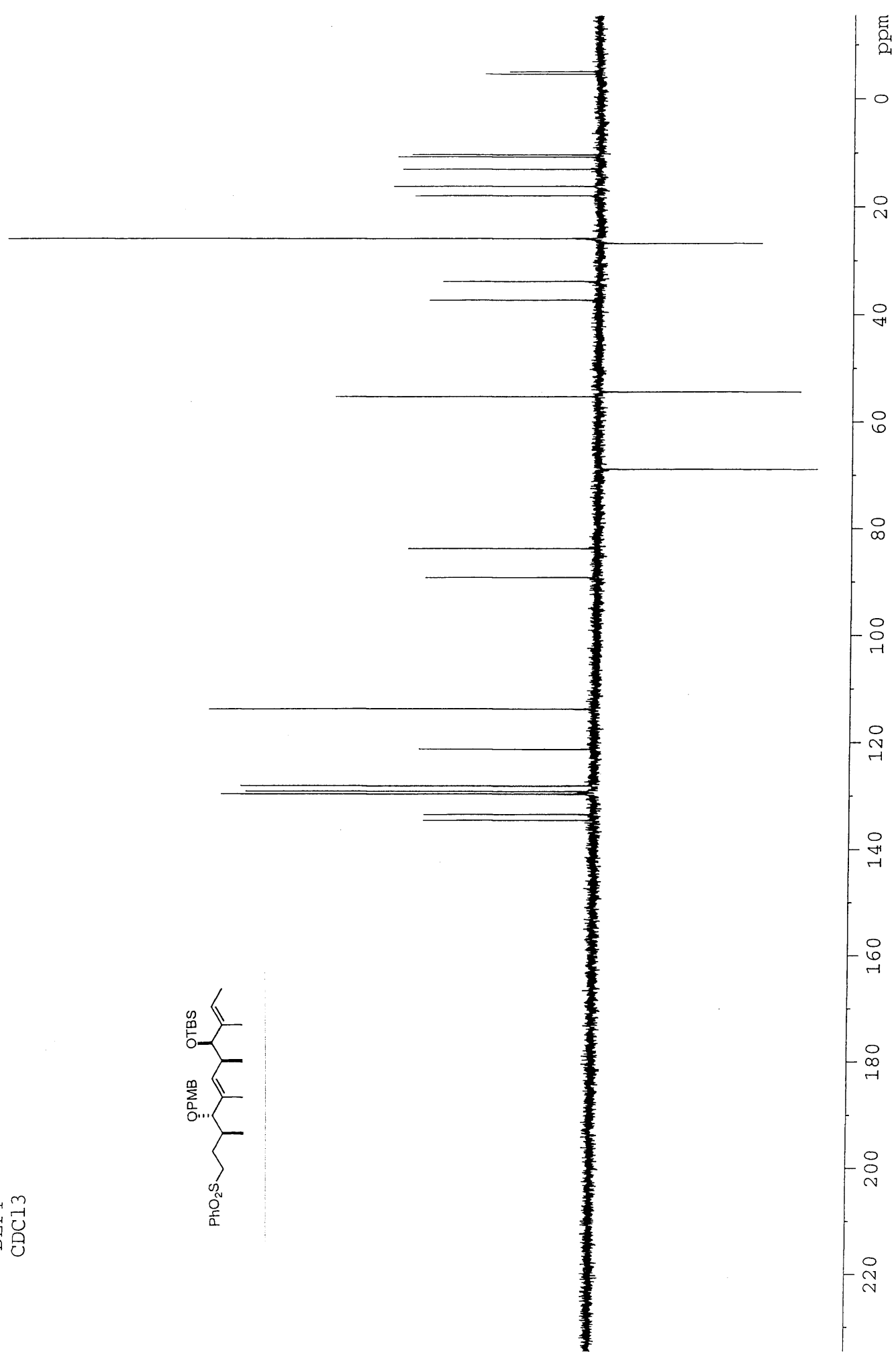
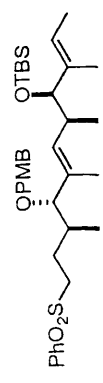
CDC13



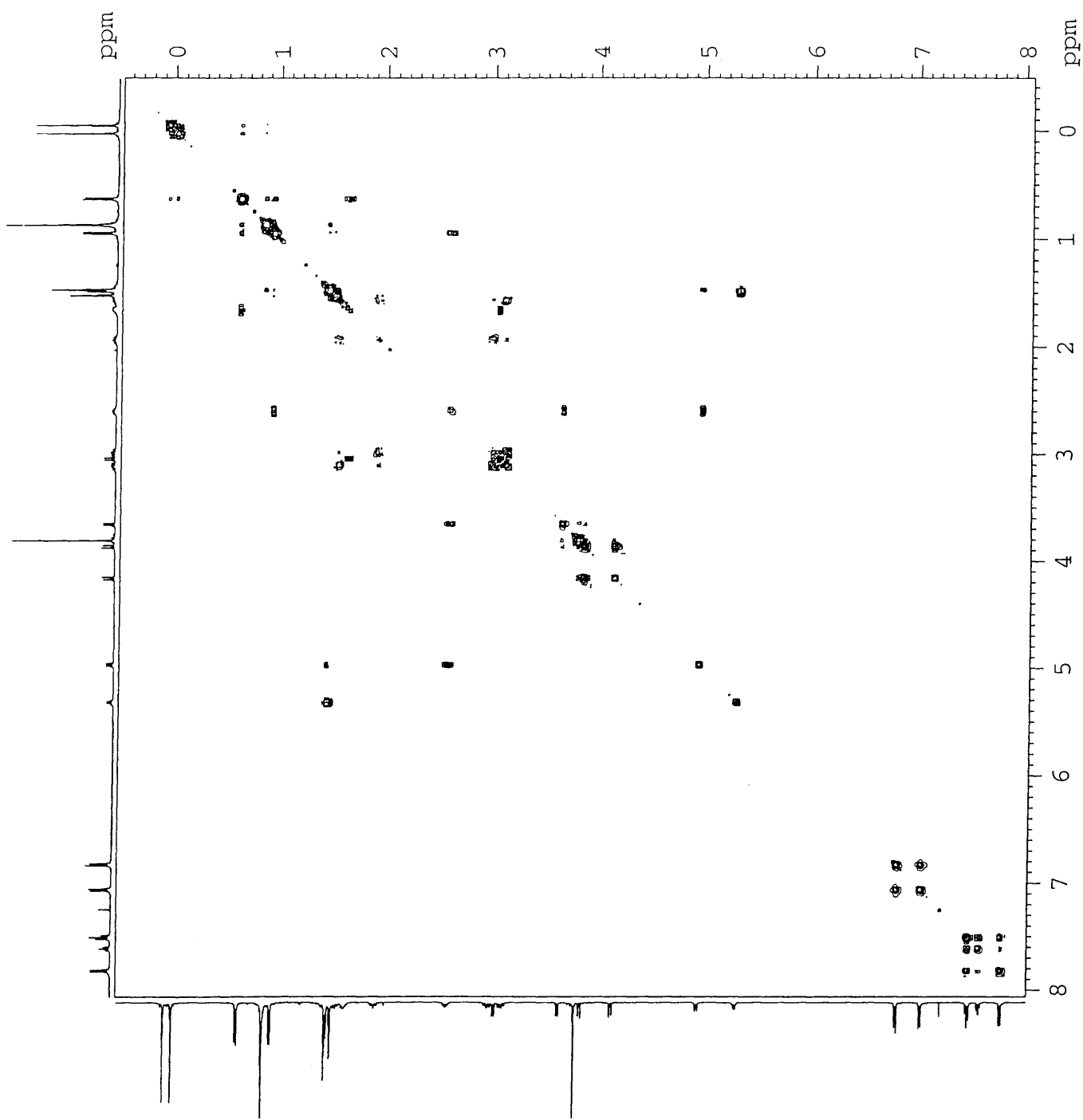
C=C(C)C(=C(C)COP(=O)(OC1=CC=CC=C1)OC2=CC=CC=C2)COP(=O)(OC3=CC=CC=C3)OC4=CC=CC=C4



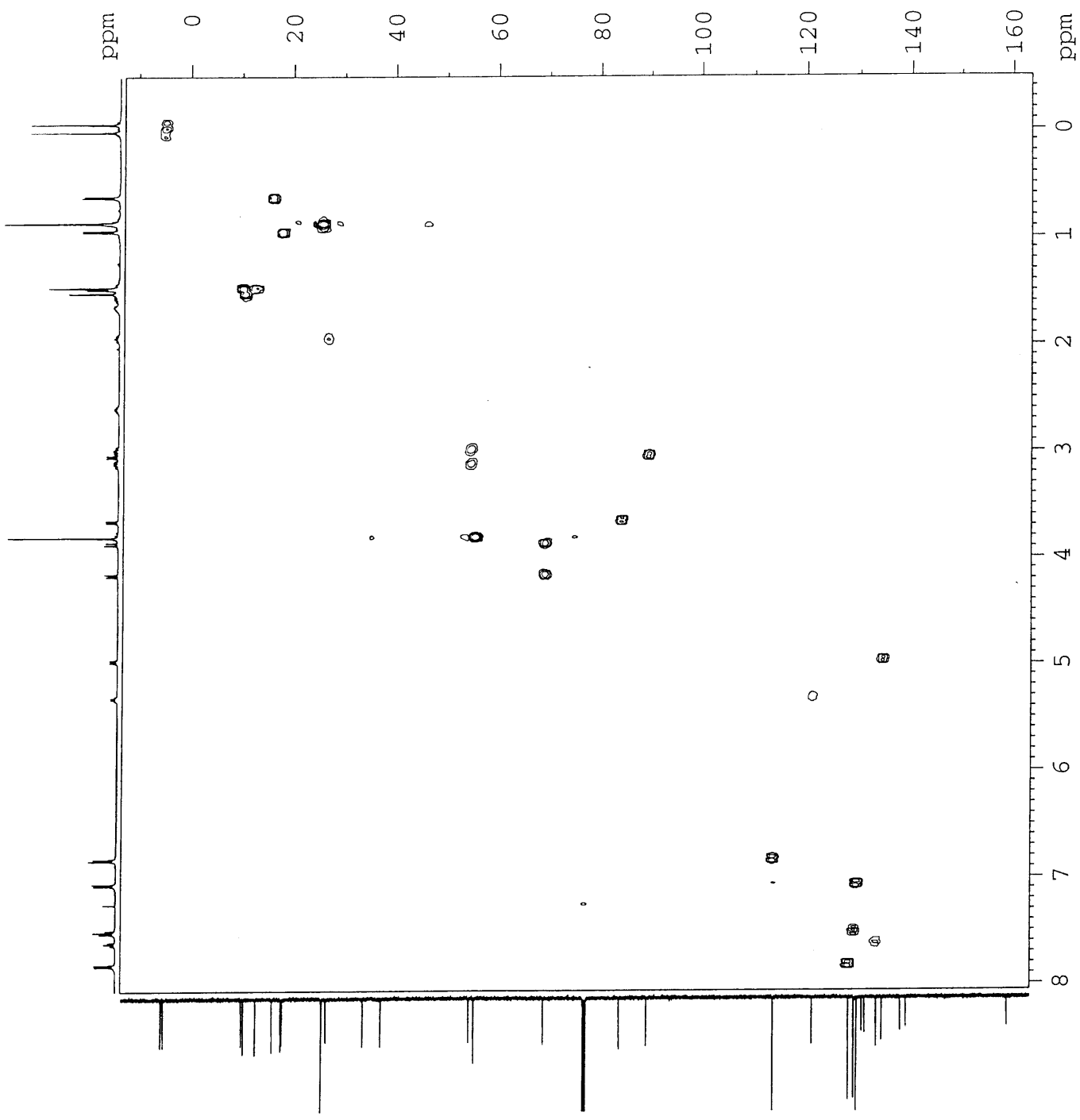
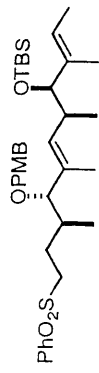
III-JG-173  
DEPT  
CDCl<sub>3</sub>

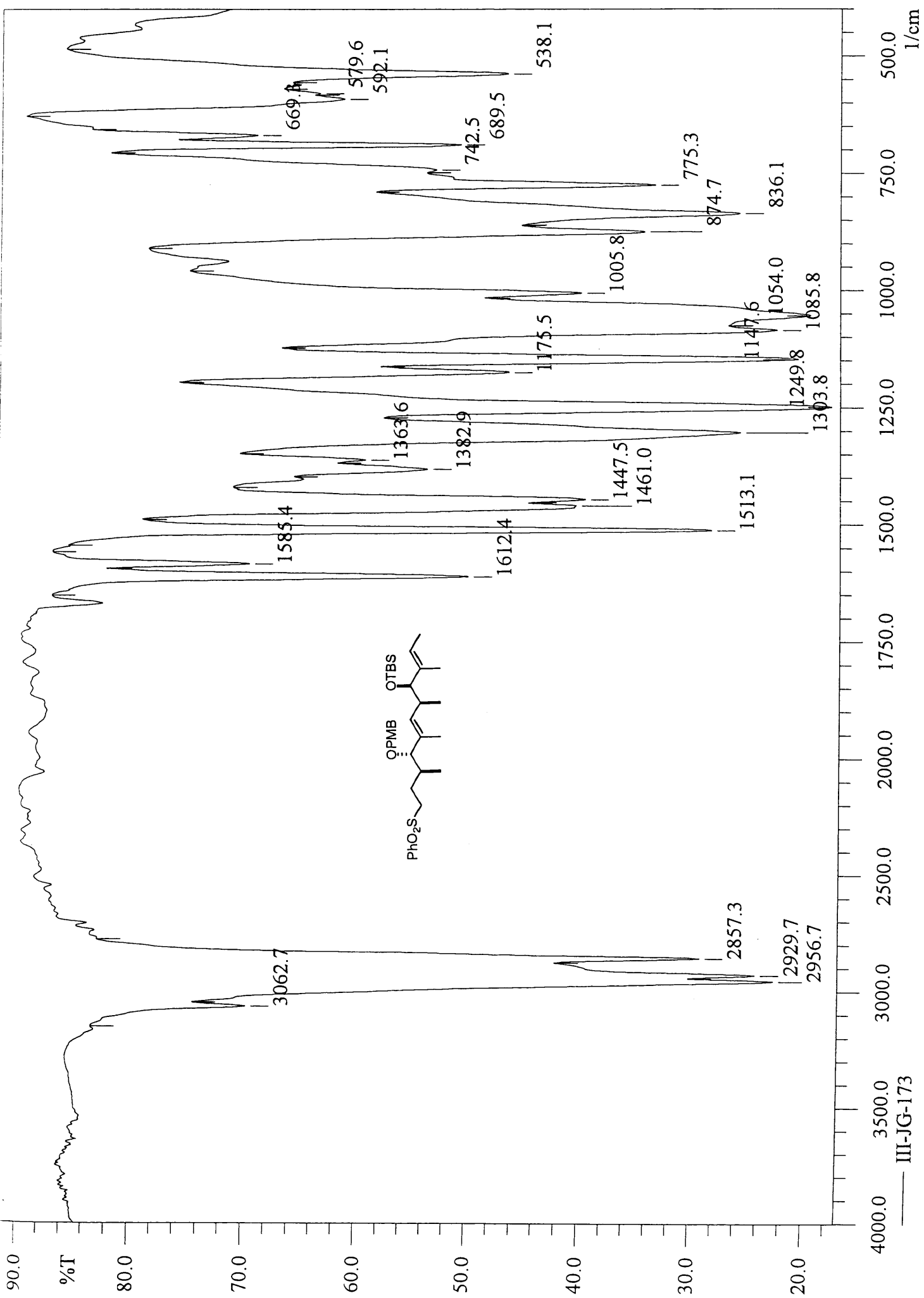


CDC13



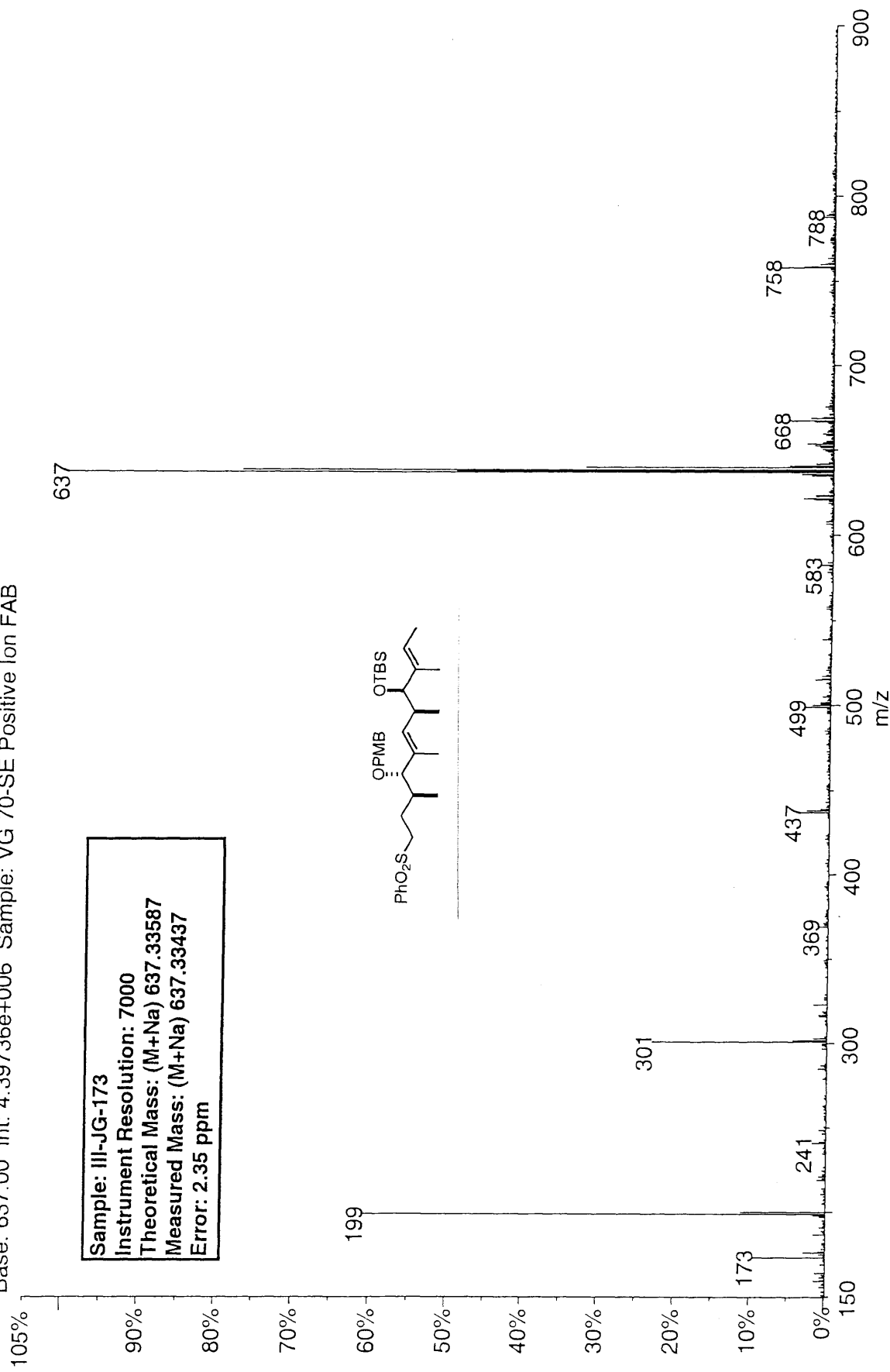
III-JG-173  
HMQC  
CDCl<sub>3</sub>



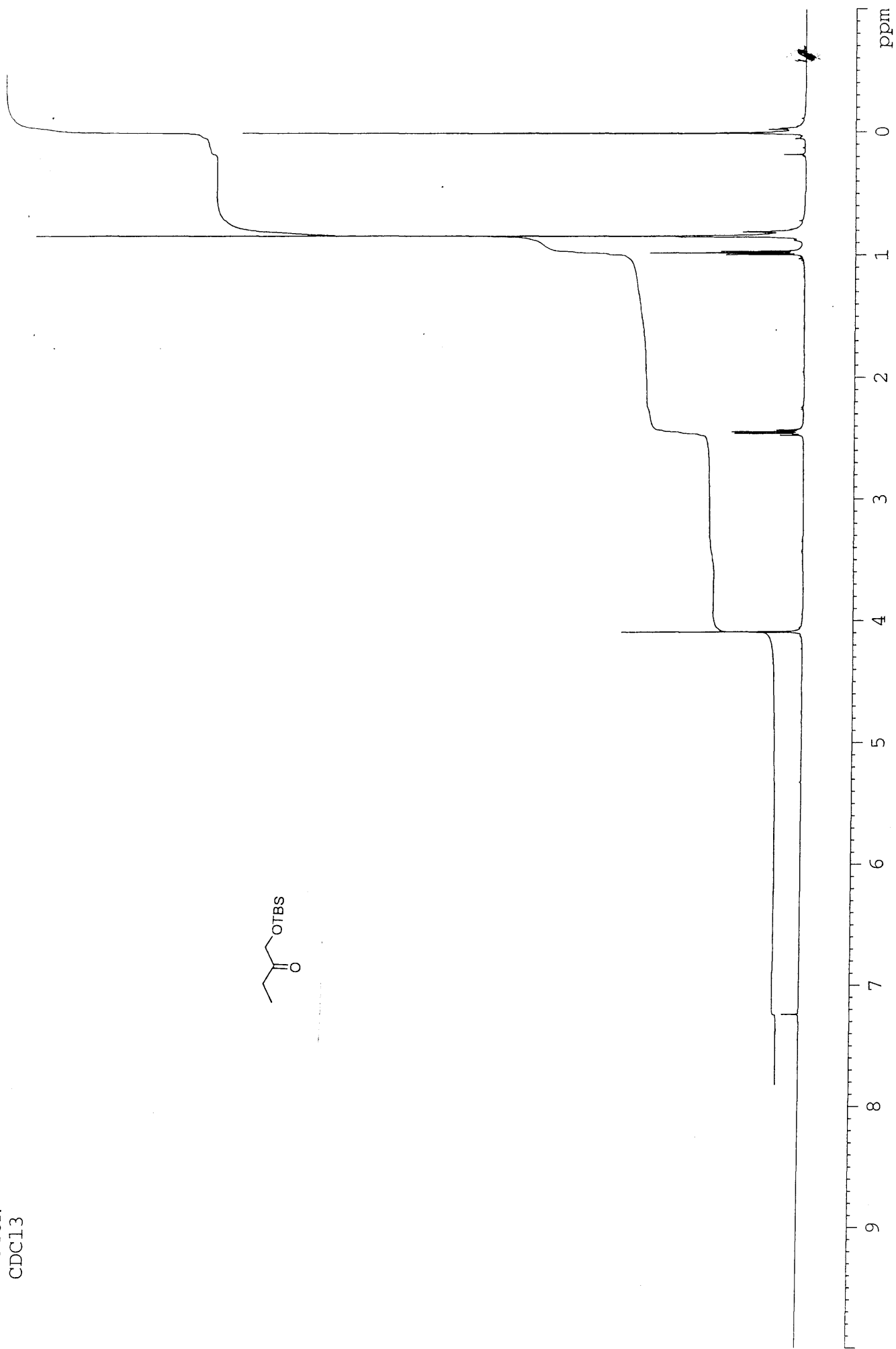
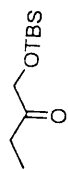


04121005: Scan Avg 85-87 (15.53 - 15.90 min) - Back  
Base: 637.00 Int: 4.39736e+006 Sample: VG 70-SE Positive Ion FAB

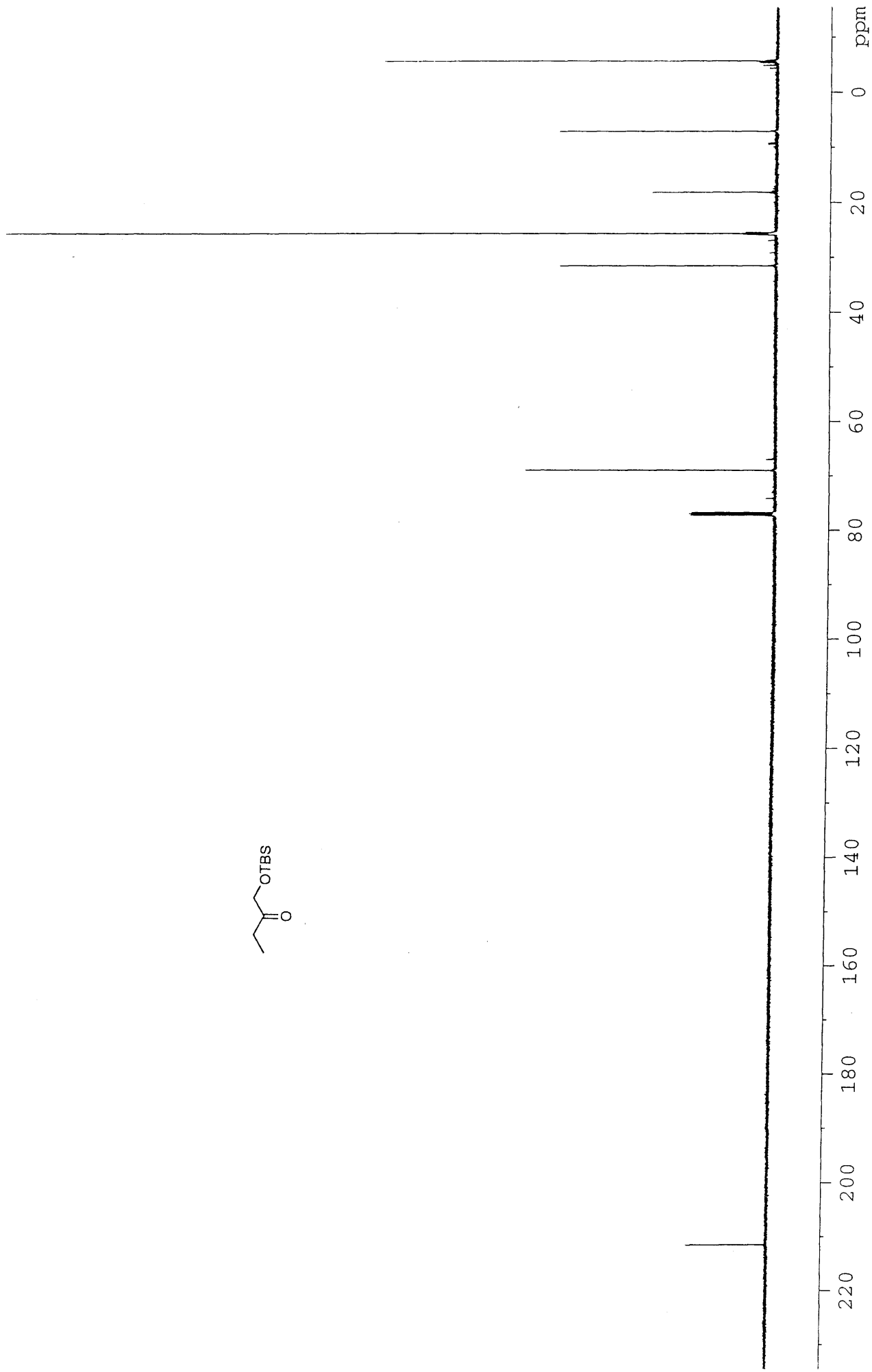
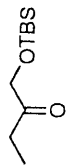
Sample: III-JG-173  
Instrument Resolution: 7000  
Theoretical Mass: (M+Na) 637.33587  
Measured Mass: (M+Na) 637.33437  
Error: 2.35 ppm



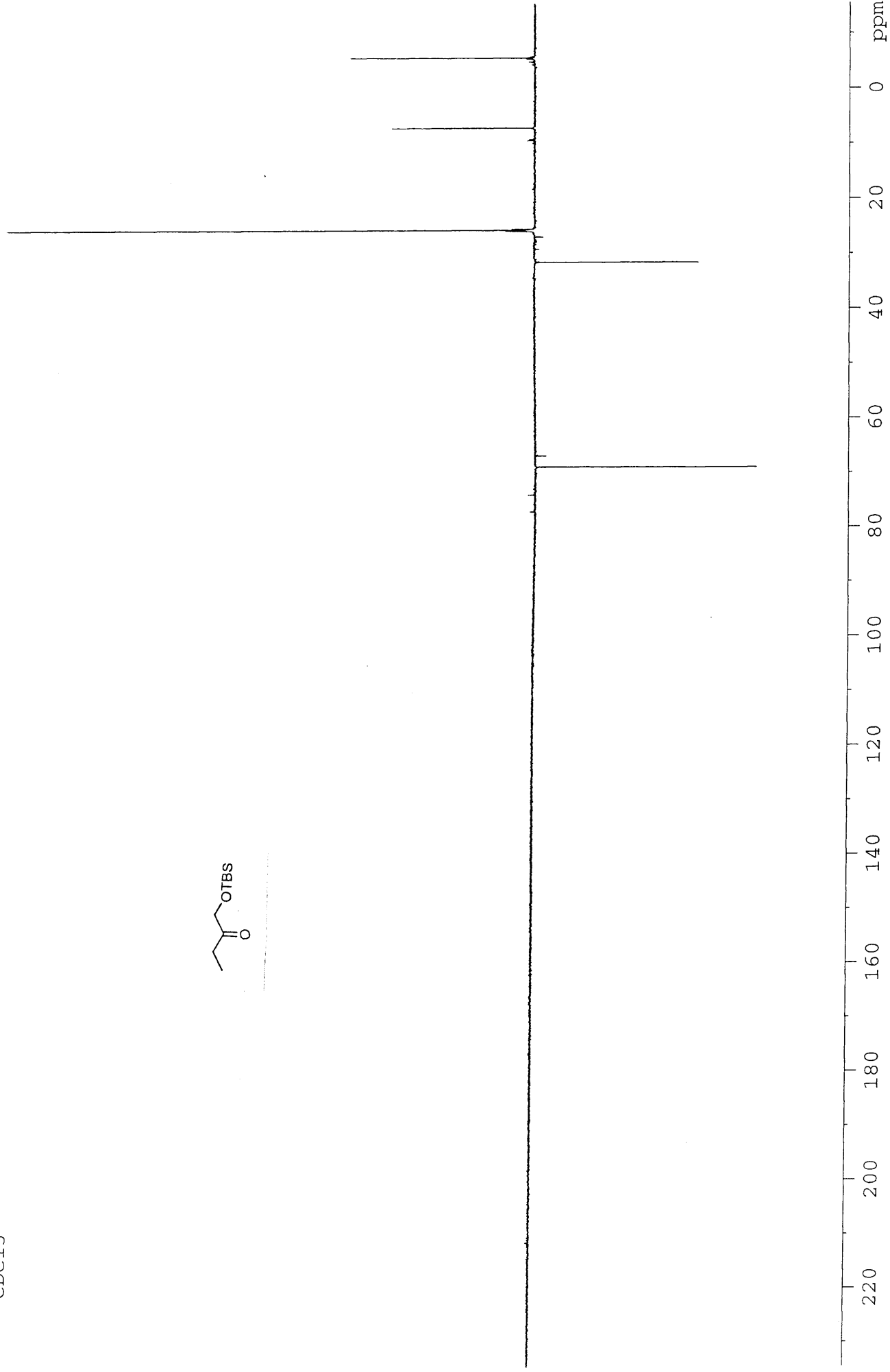
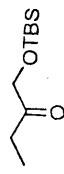
III-JG-127  
PROTON  
CDCl<sub>3</sub>



III-JG-127  
CARBON  
CDCl<sub>3</sub>

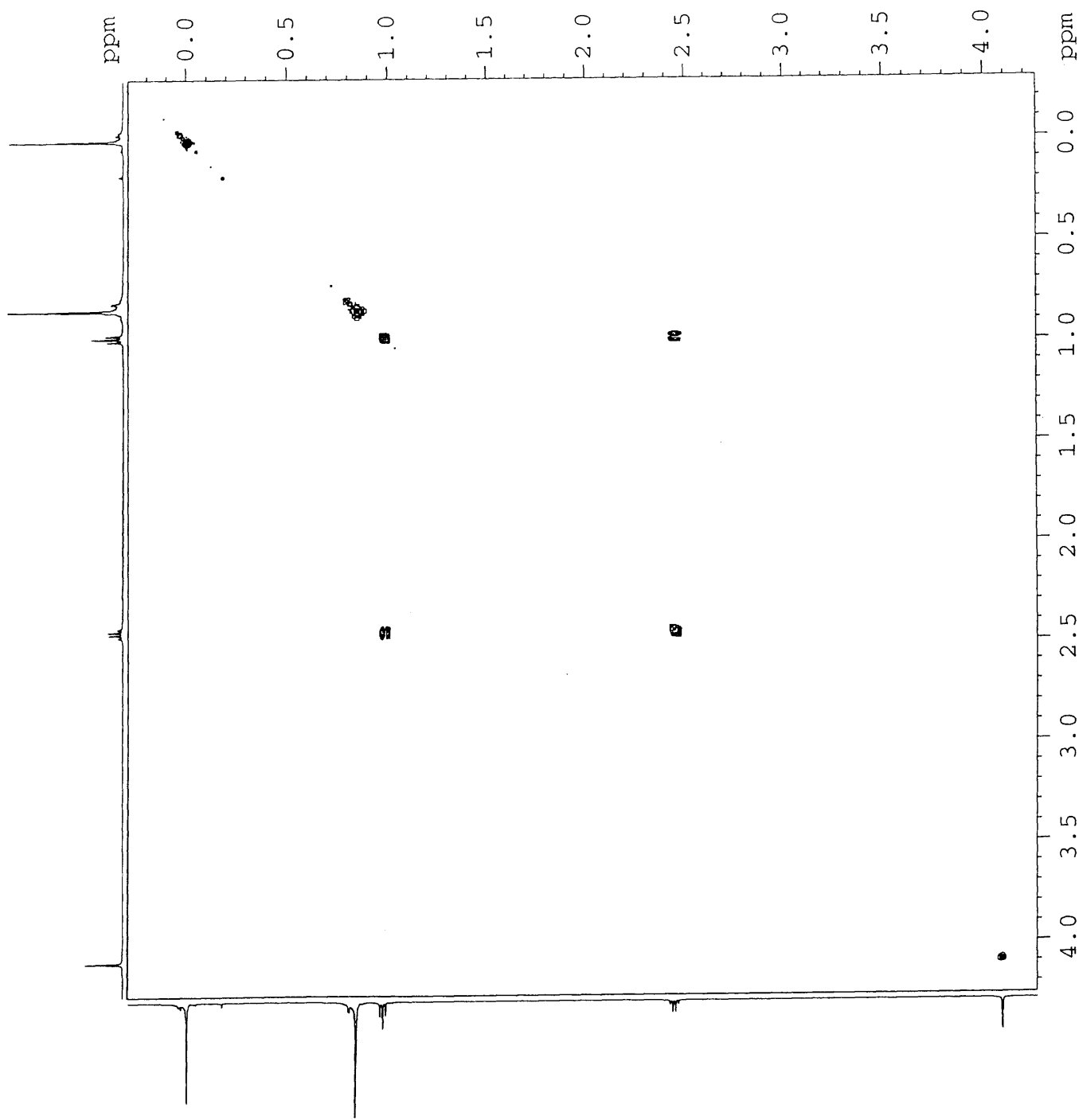
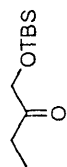


III-JG-127  
DEPT  
CDCl<sub>3</sub>

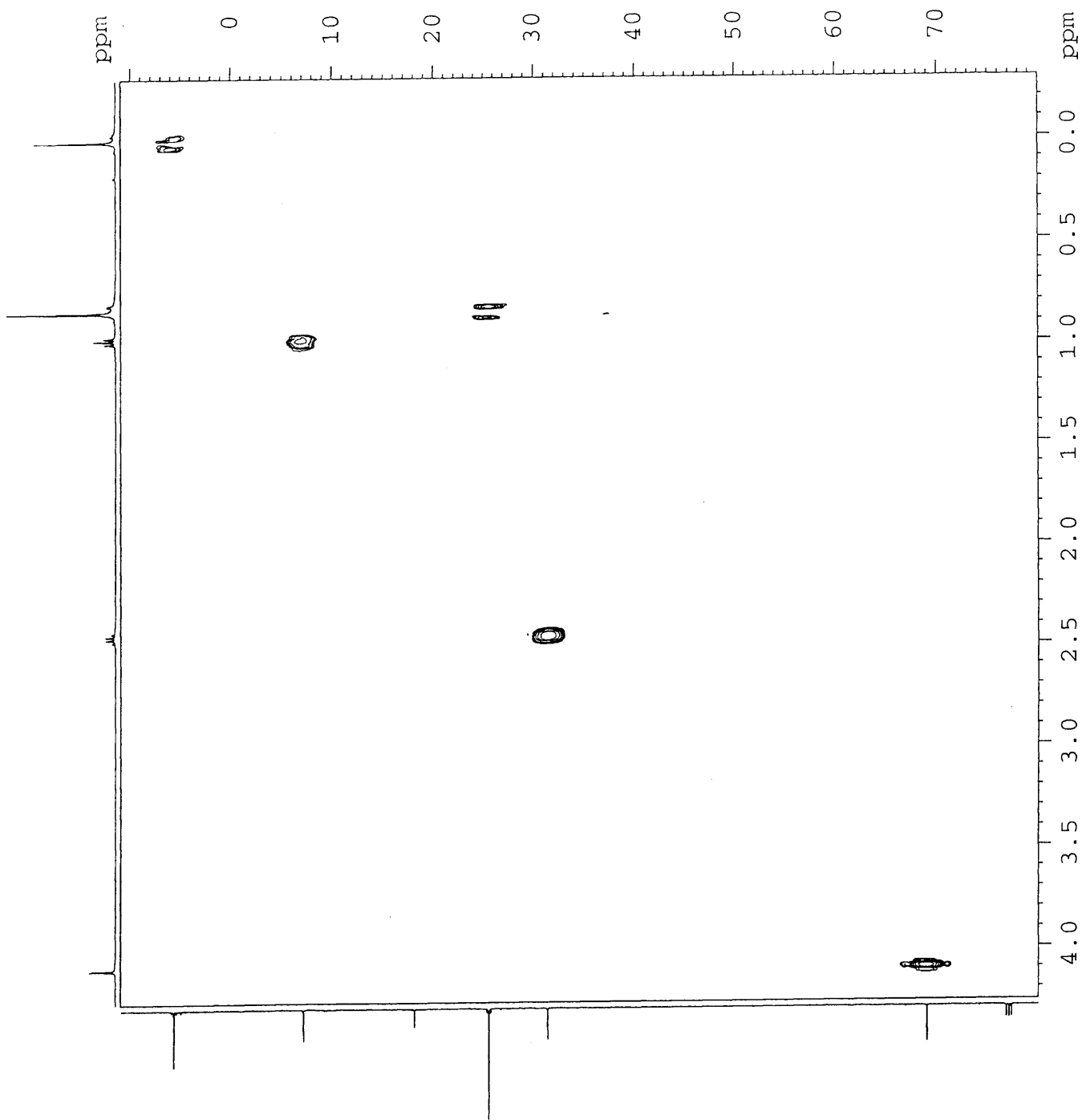
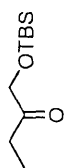


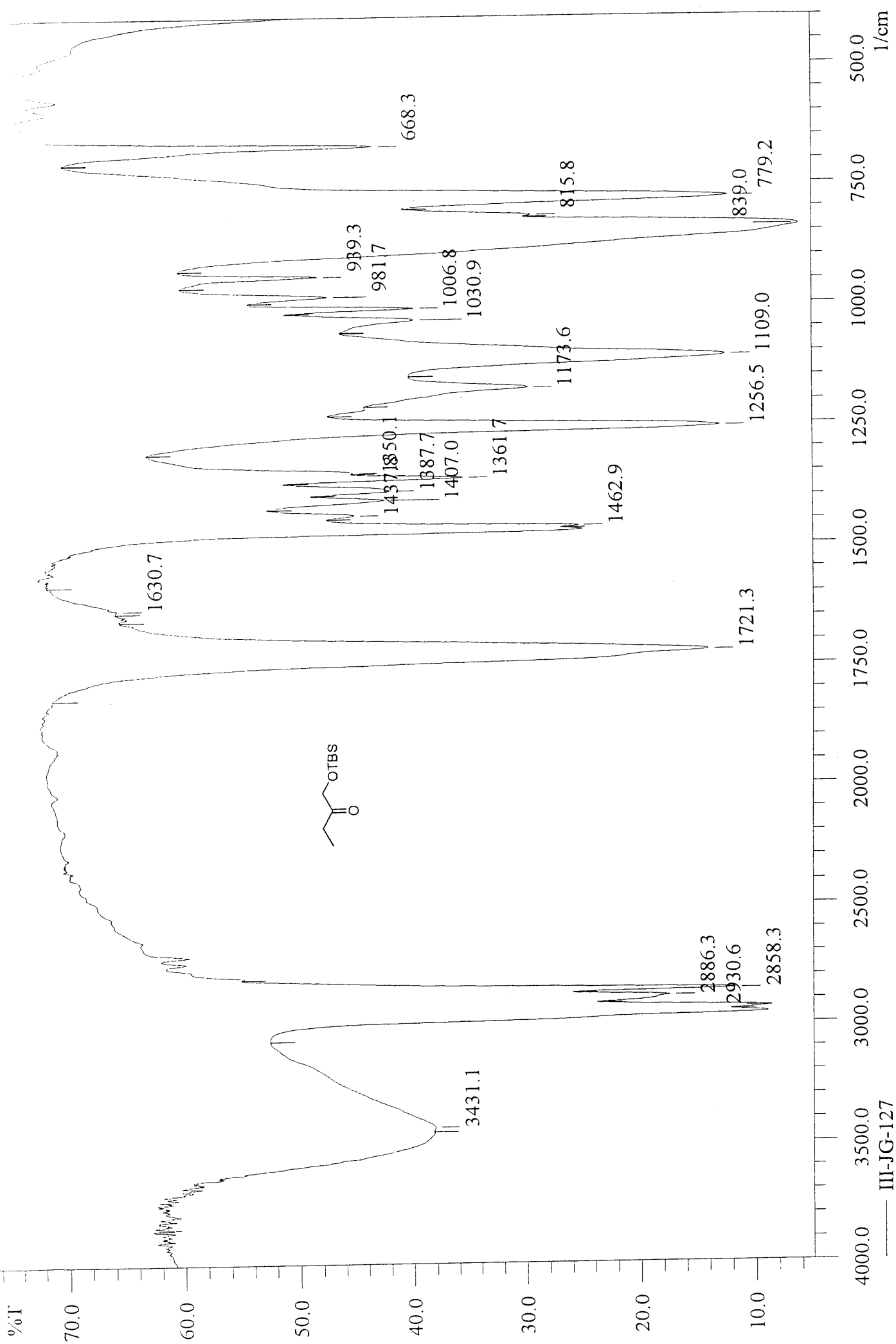


III-JG-127  
COSY  
CDCl<sub>3</sub>

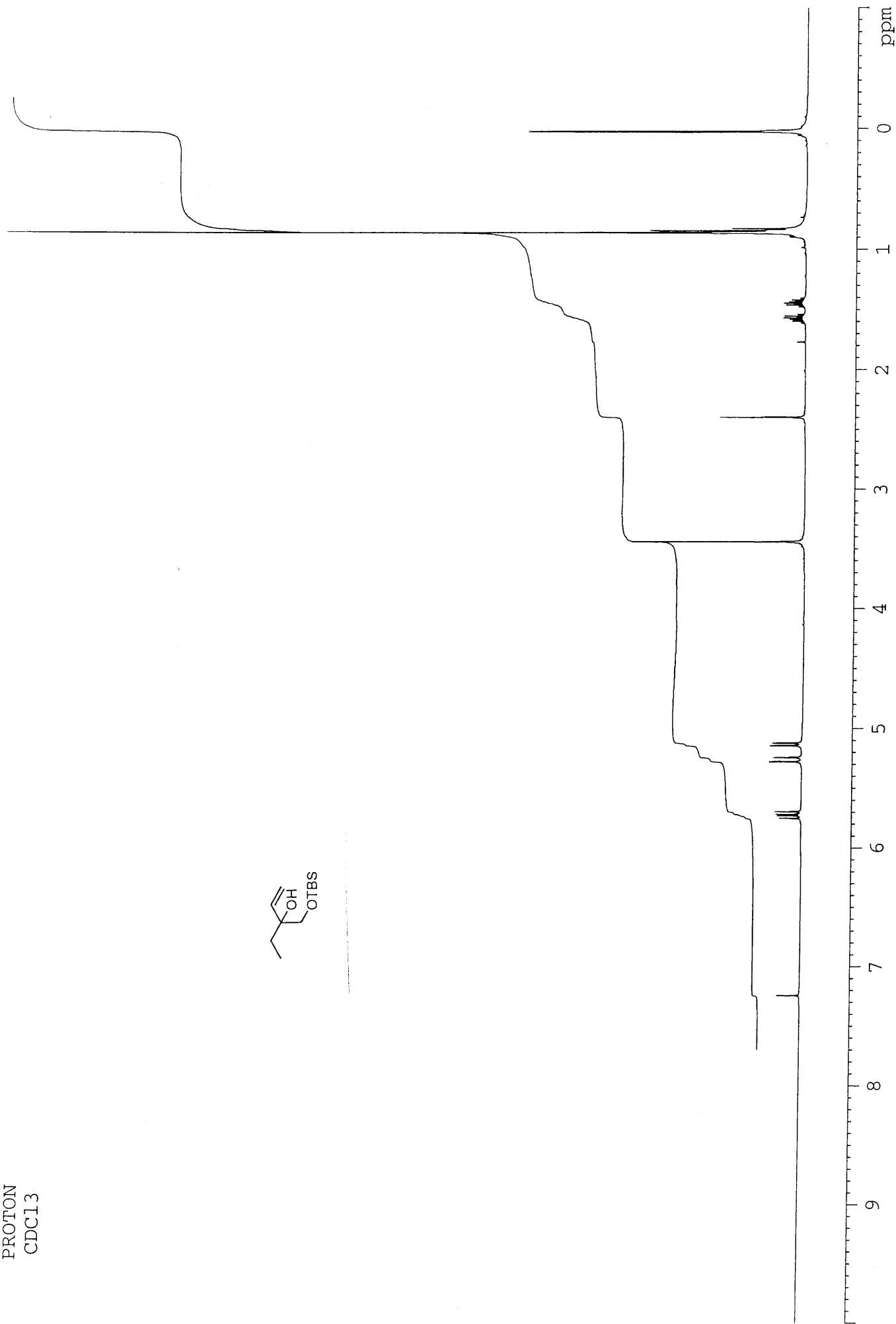
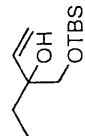


III-JG-127  
HMQC  
CDCl<sub>3</sub>





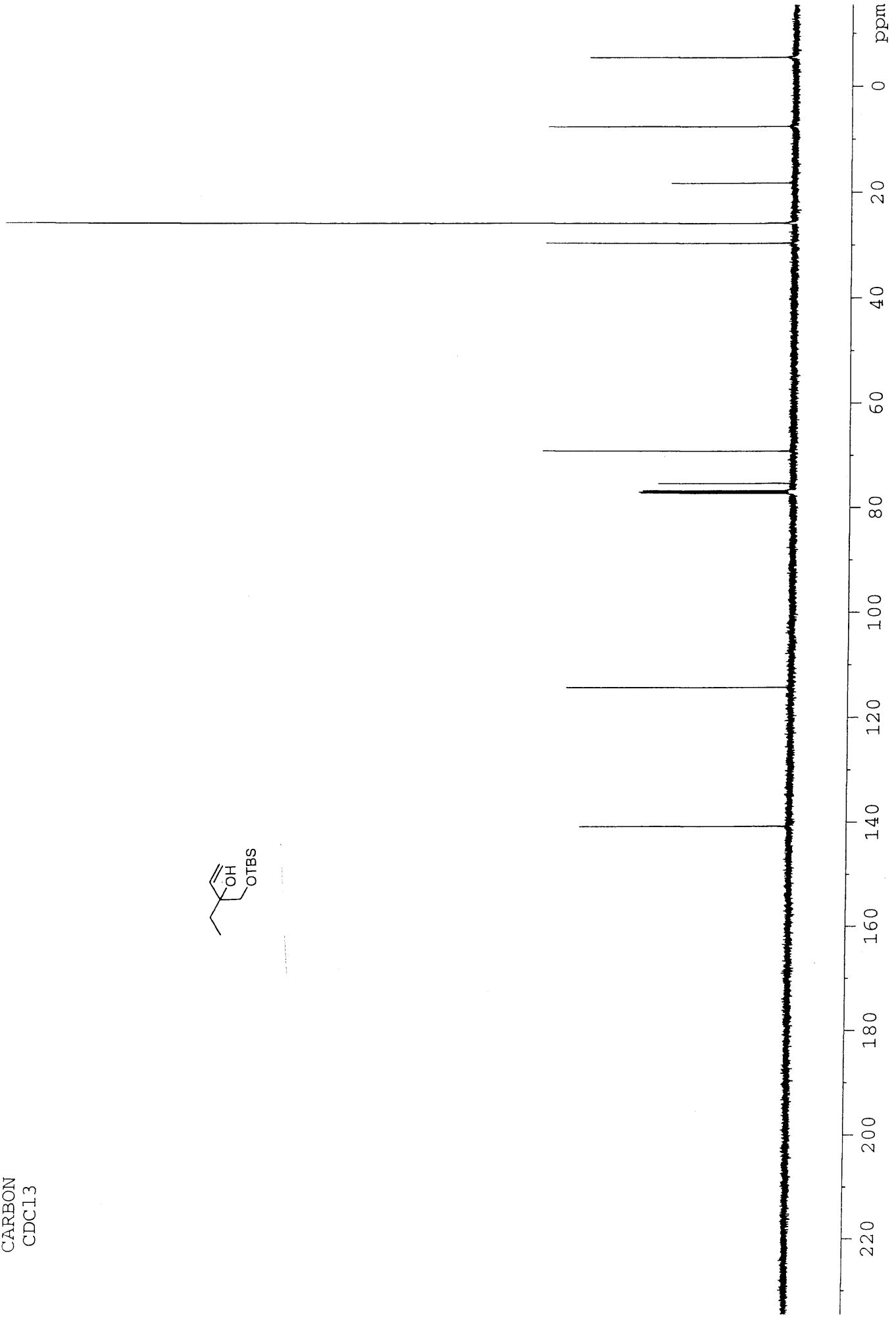
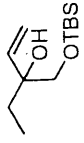
III-JG-133  
PROTON  
CDCl<sub>3</sub>



III-JG-133

# CARBON

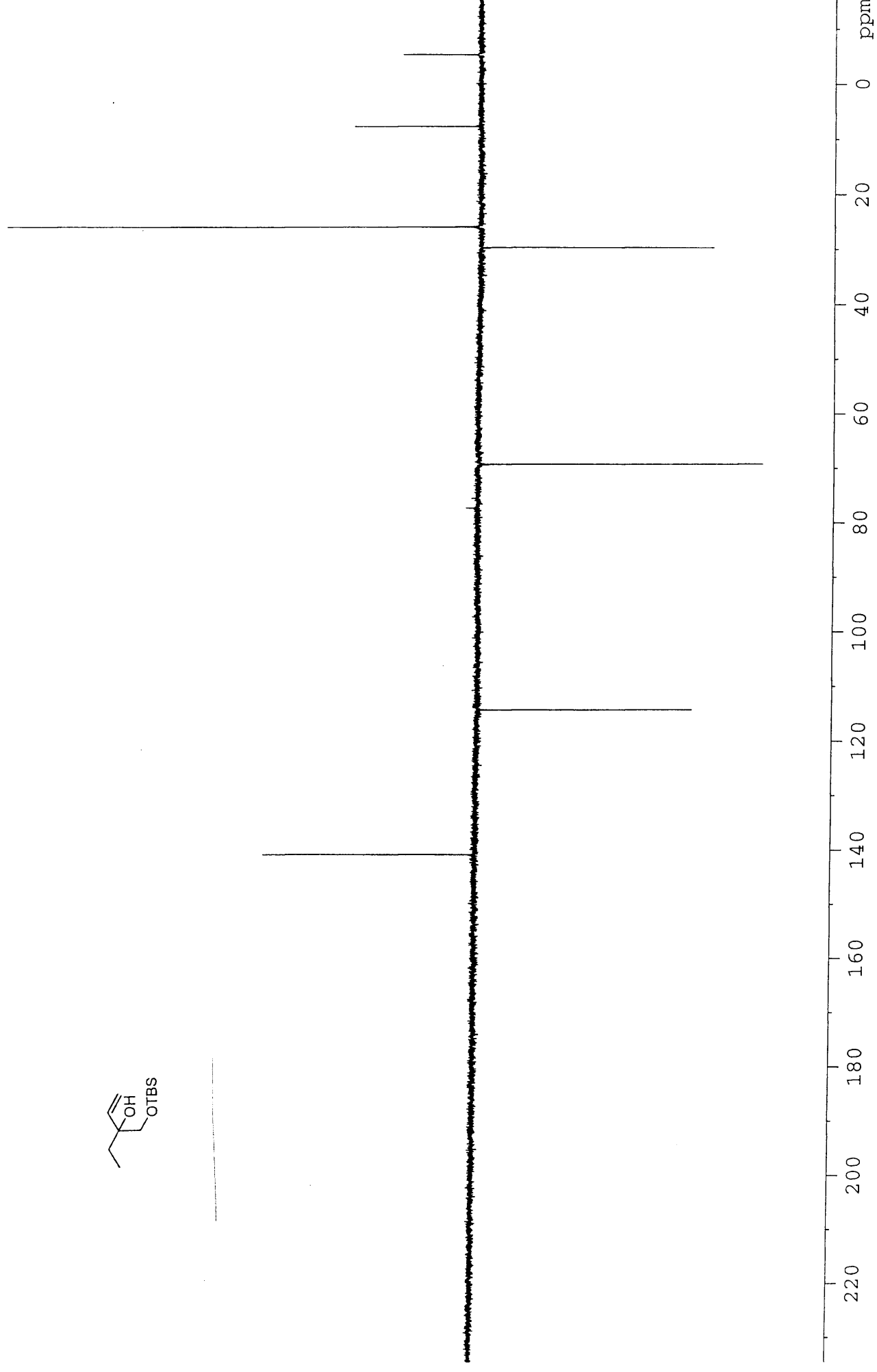
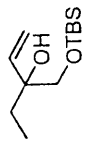
CDC13



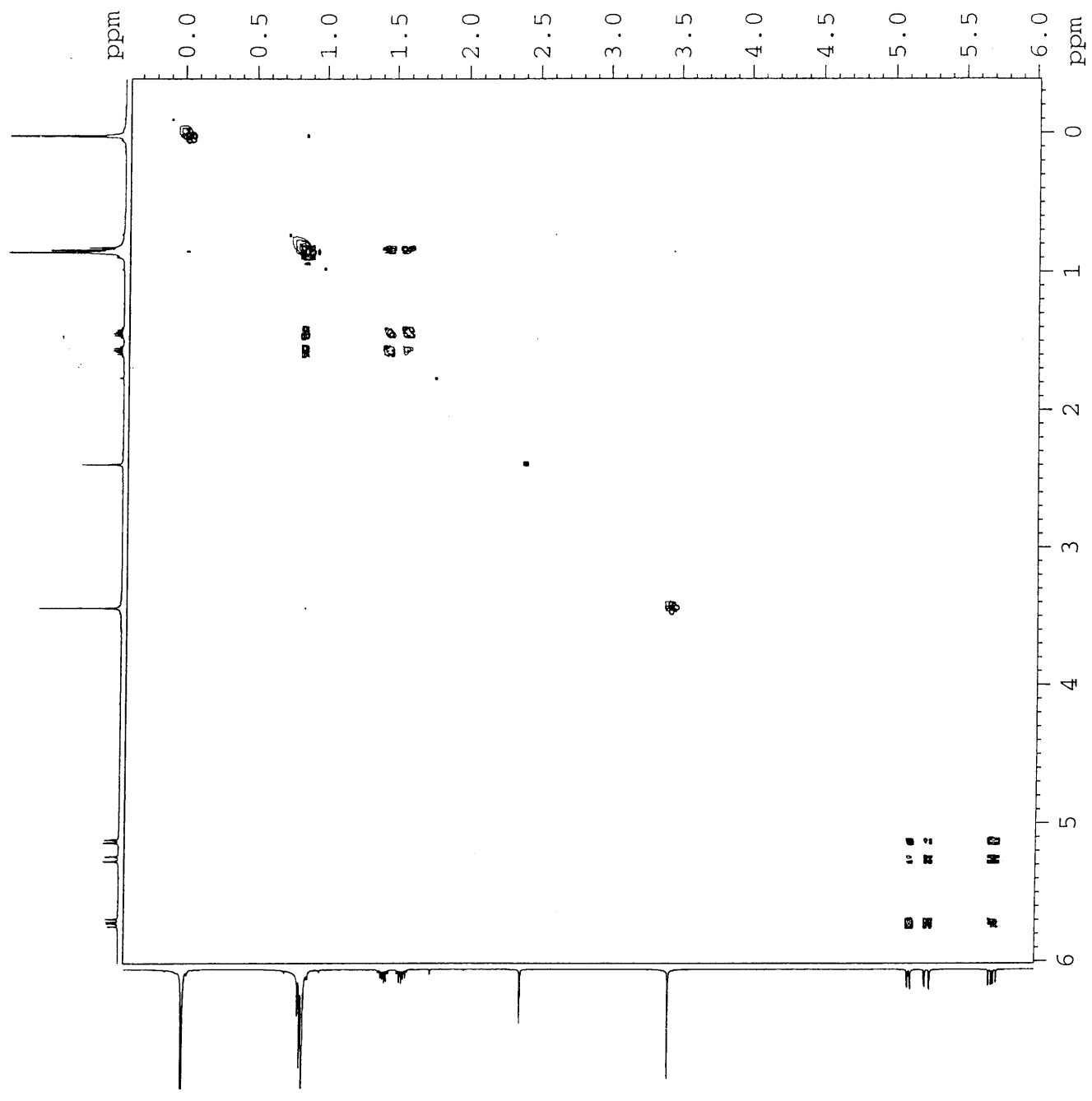
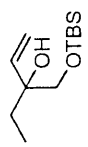
III-JG-133

DEPT

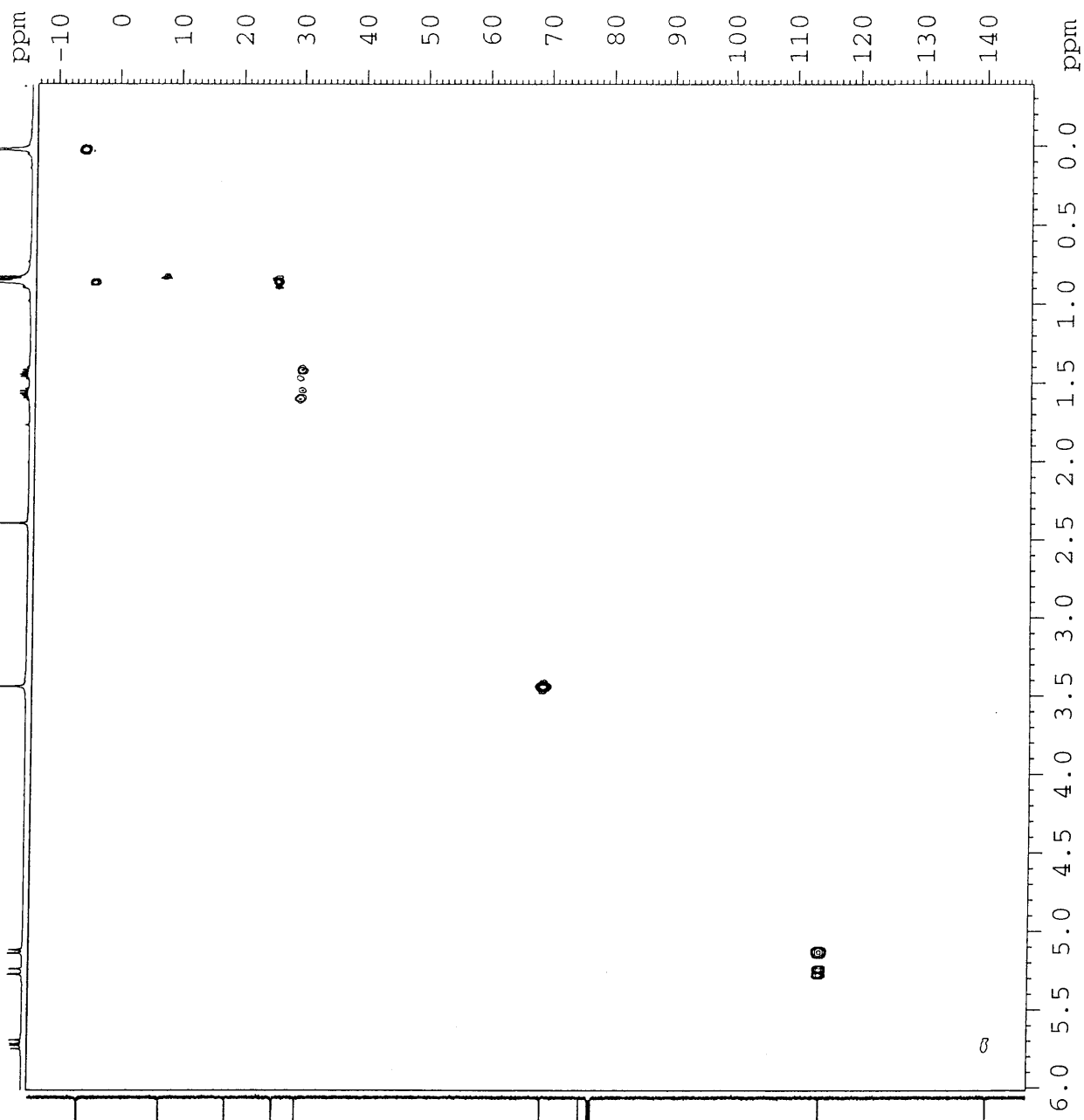
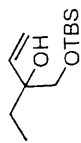
CDCl<sub>3</sub>



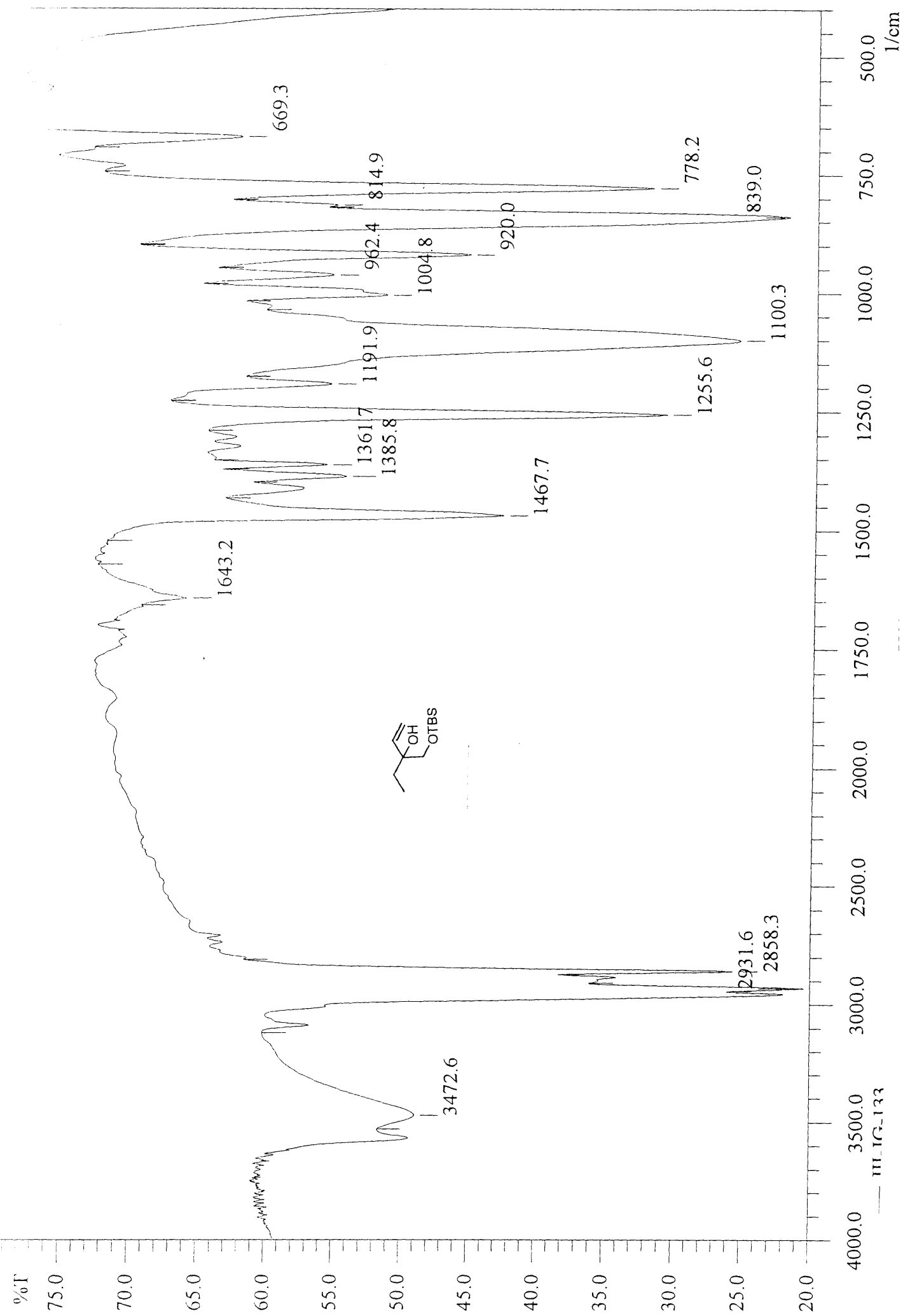
III-JG-133  
COSY  
CDCl3



CDC13

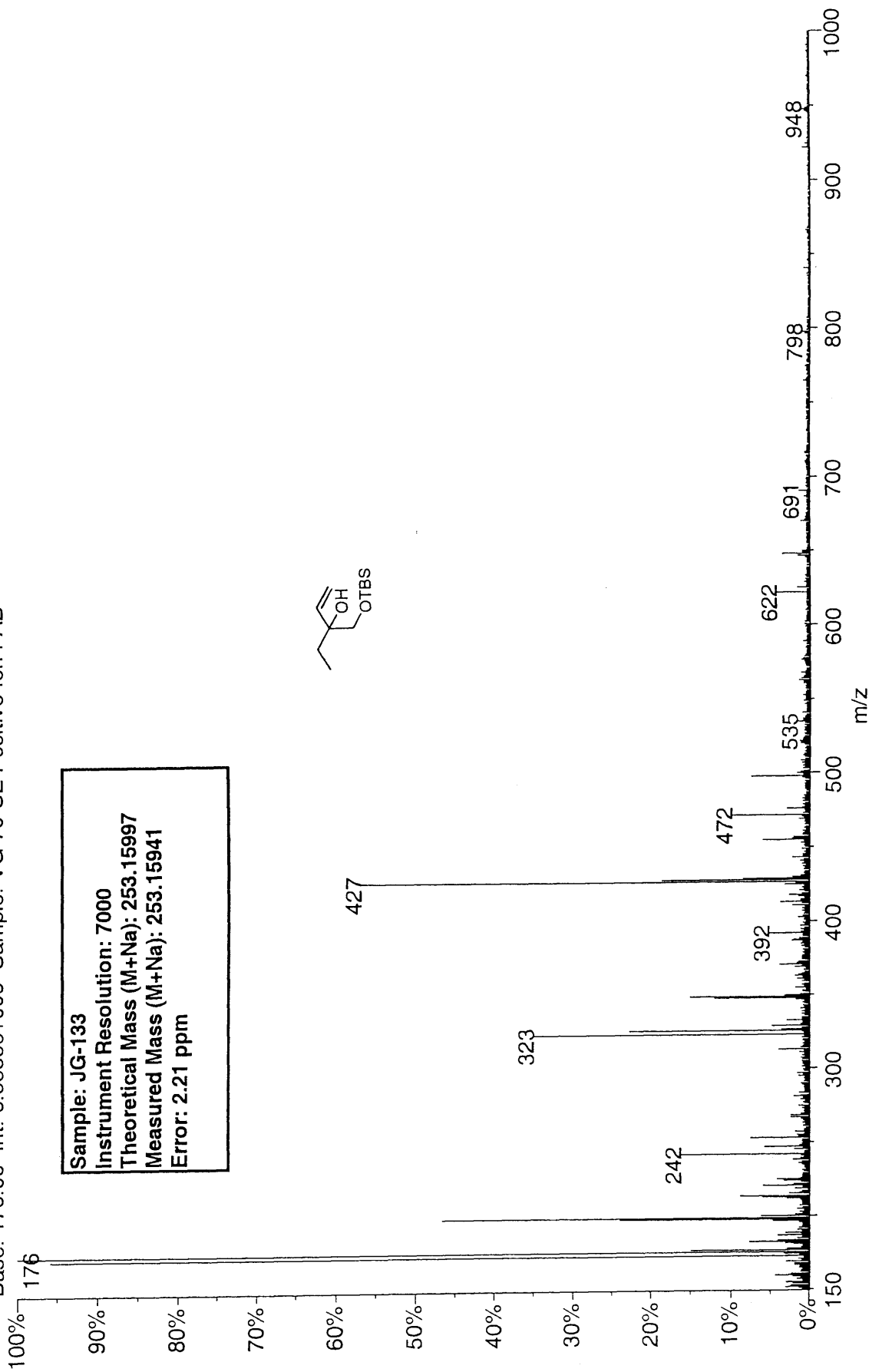
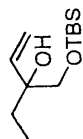




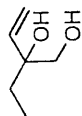


02170706: Scan 509 (101.70 min)  
Base: 176.00 Int: 6.5535e+006 Sample: VG 70-SE Positive Ion FAB

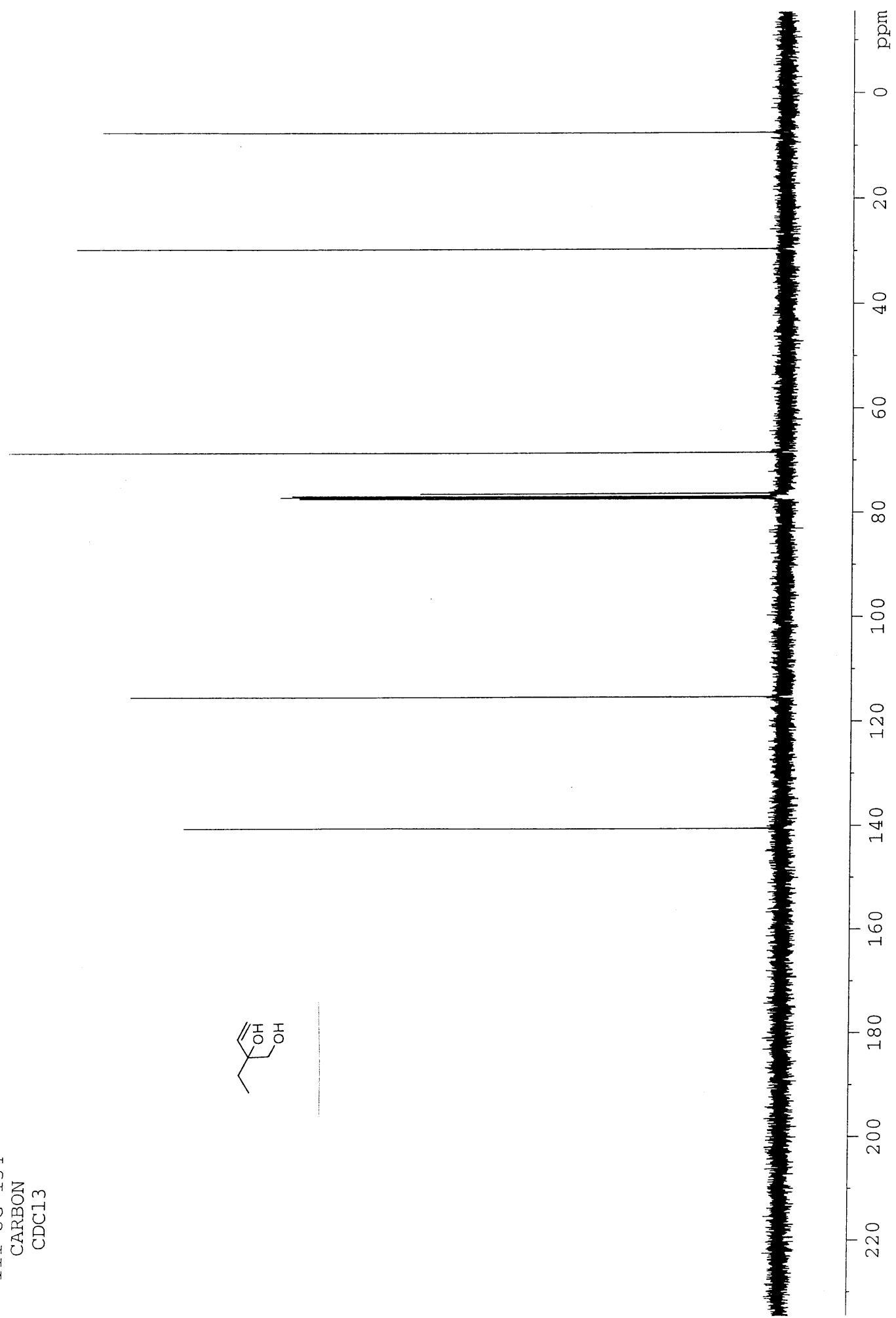
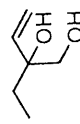
Sample: JG-133  
Instrument Resolution: 7000  
Theoretical Mass (M+Na): 253.15997  
Measured Mass (M+Na): 253.15941  
Error: 2.21 ppm



III-JG-134  
PROTON  
CDCl<sub>3</sub>



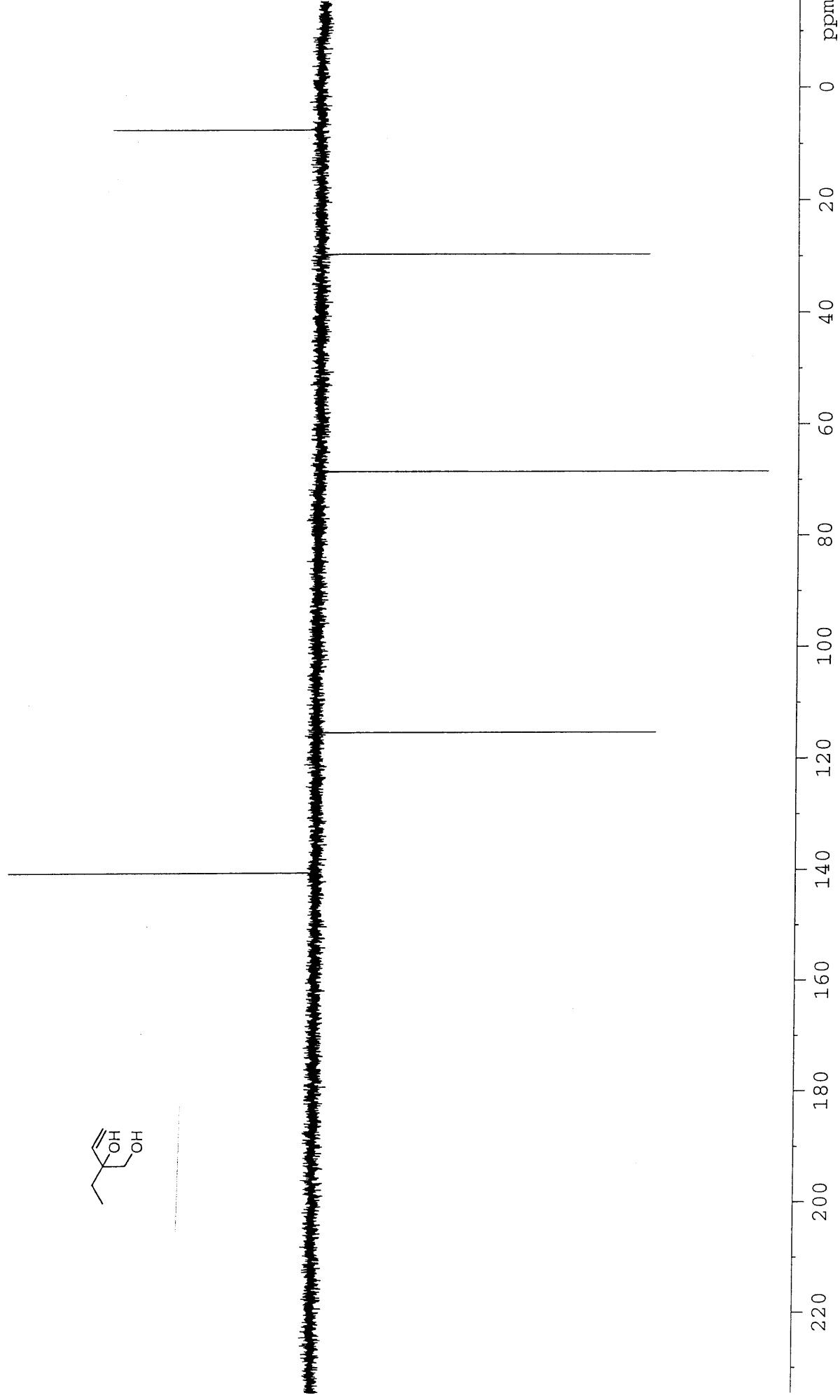
III-JG-134  
CARBON  
CDCl<sub>3</sub>



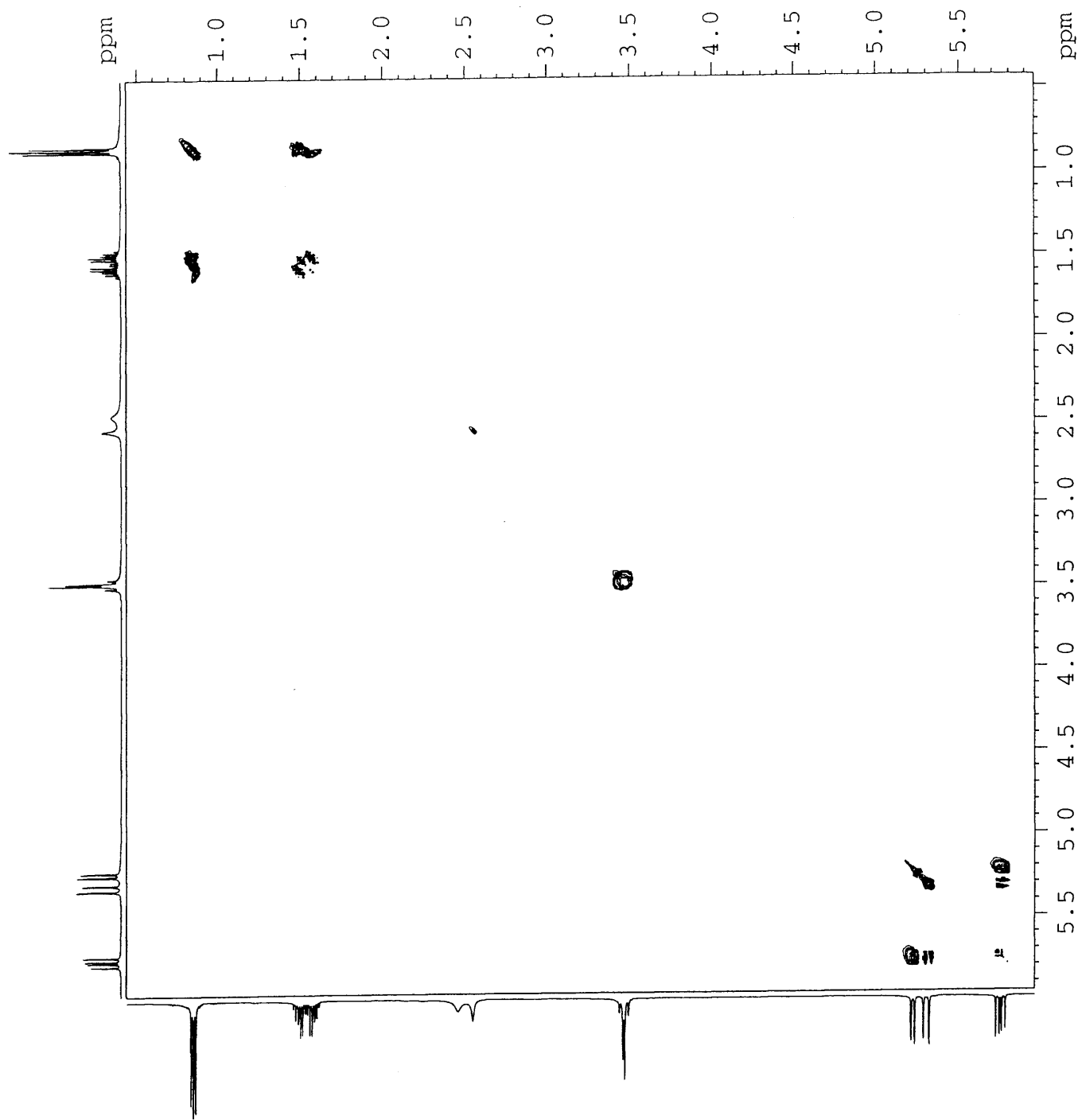
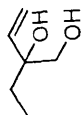
III-JG-134

DEPT

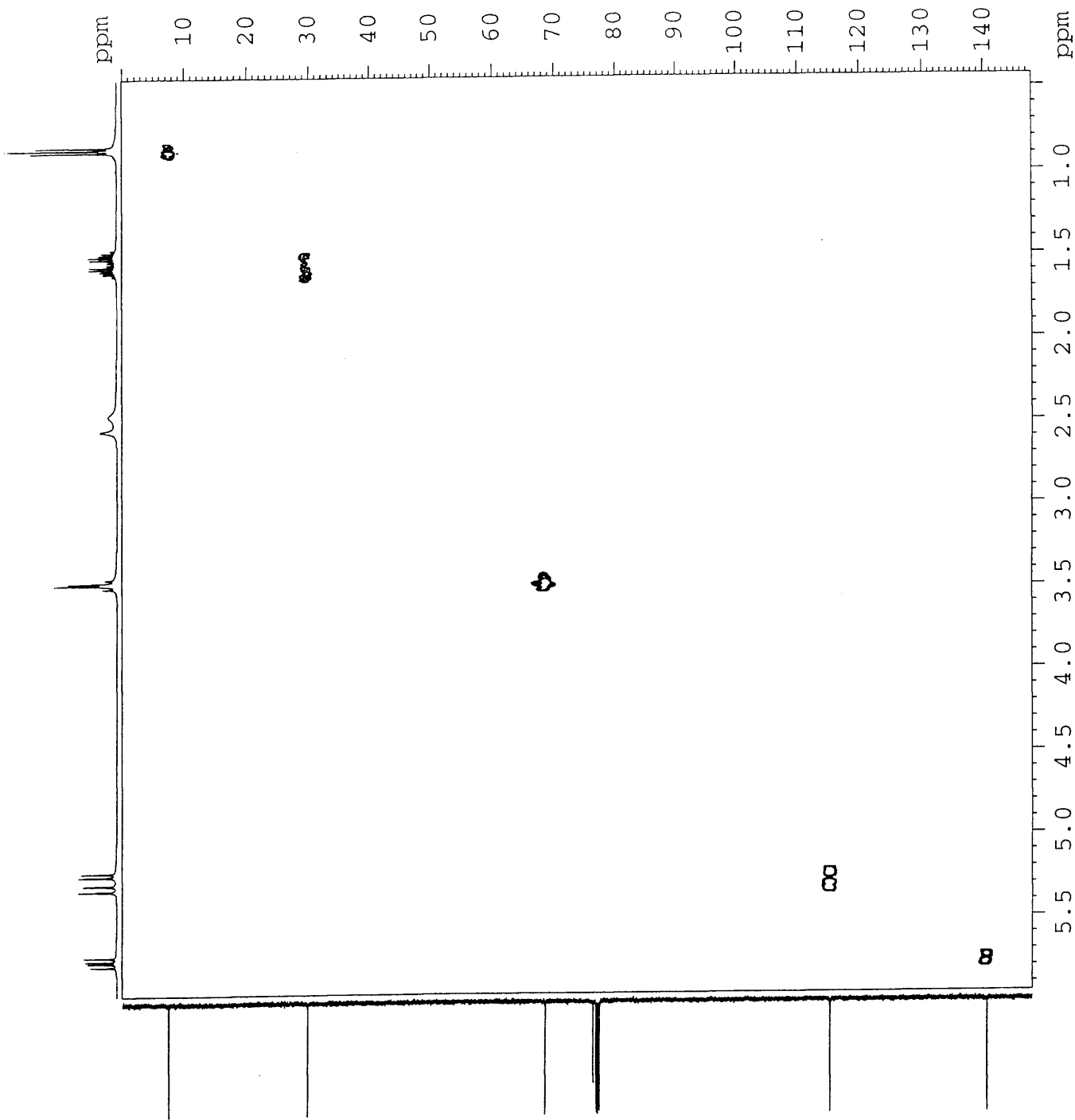
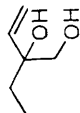
CDC13

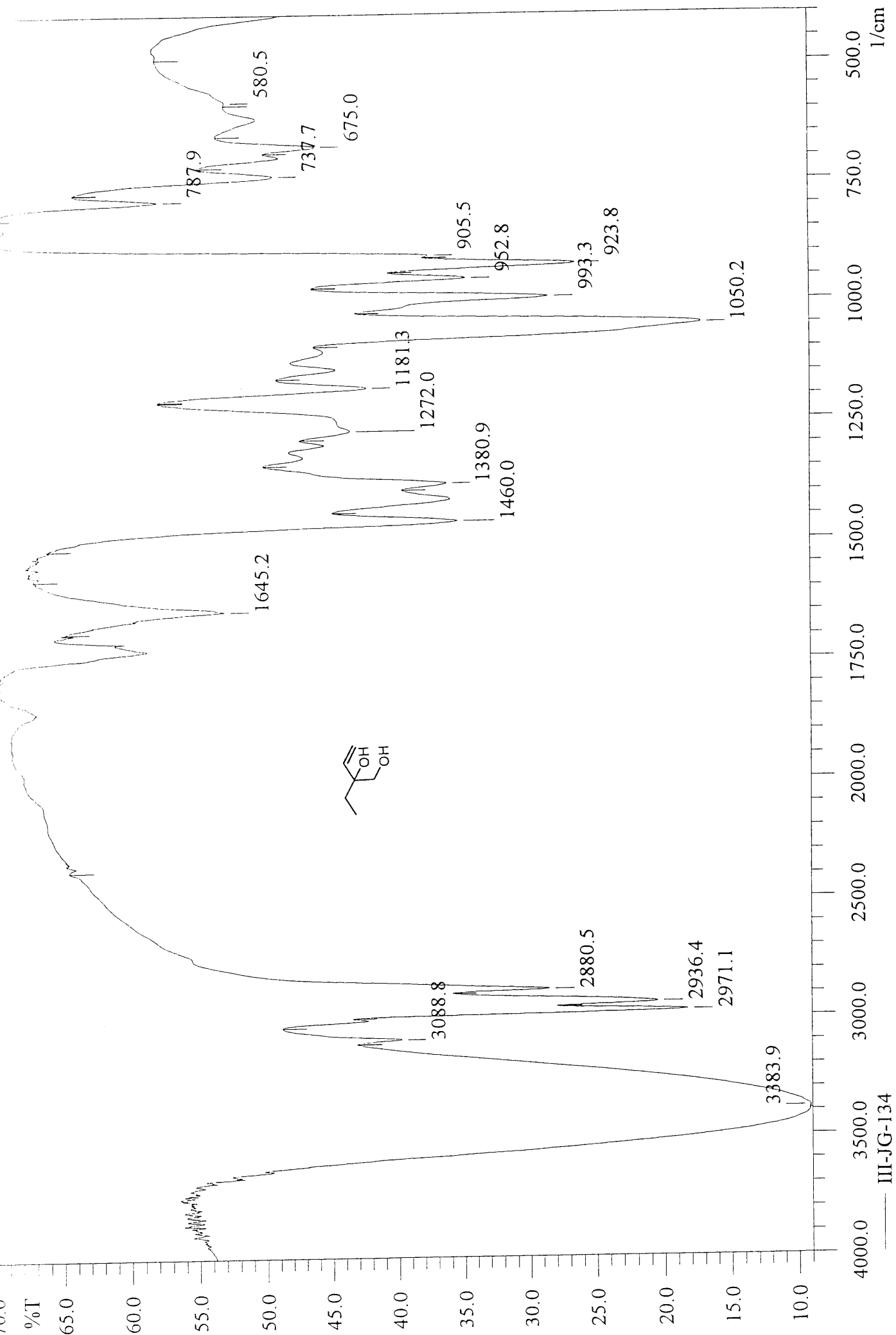


III-JG-134  
COSY  
CDCl3



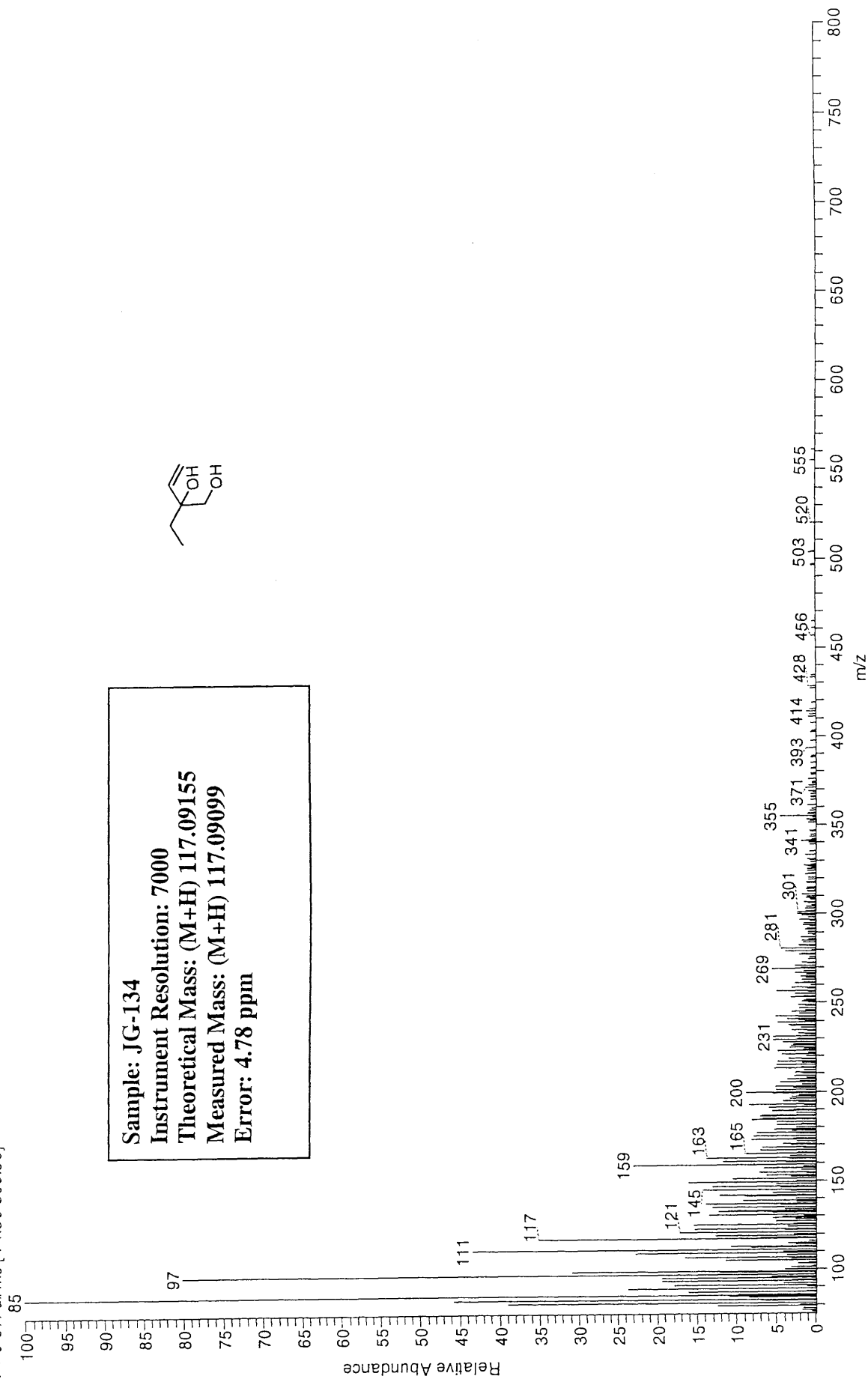
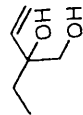
111-JG-134  
HMQC  
CDCl3



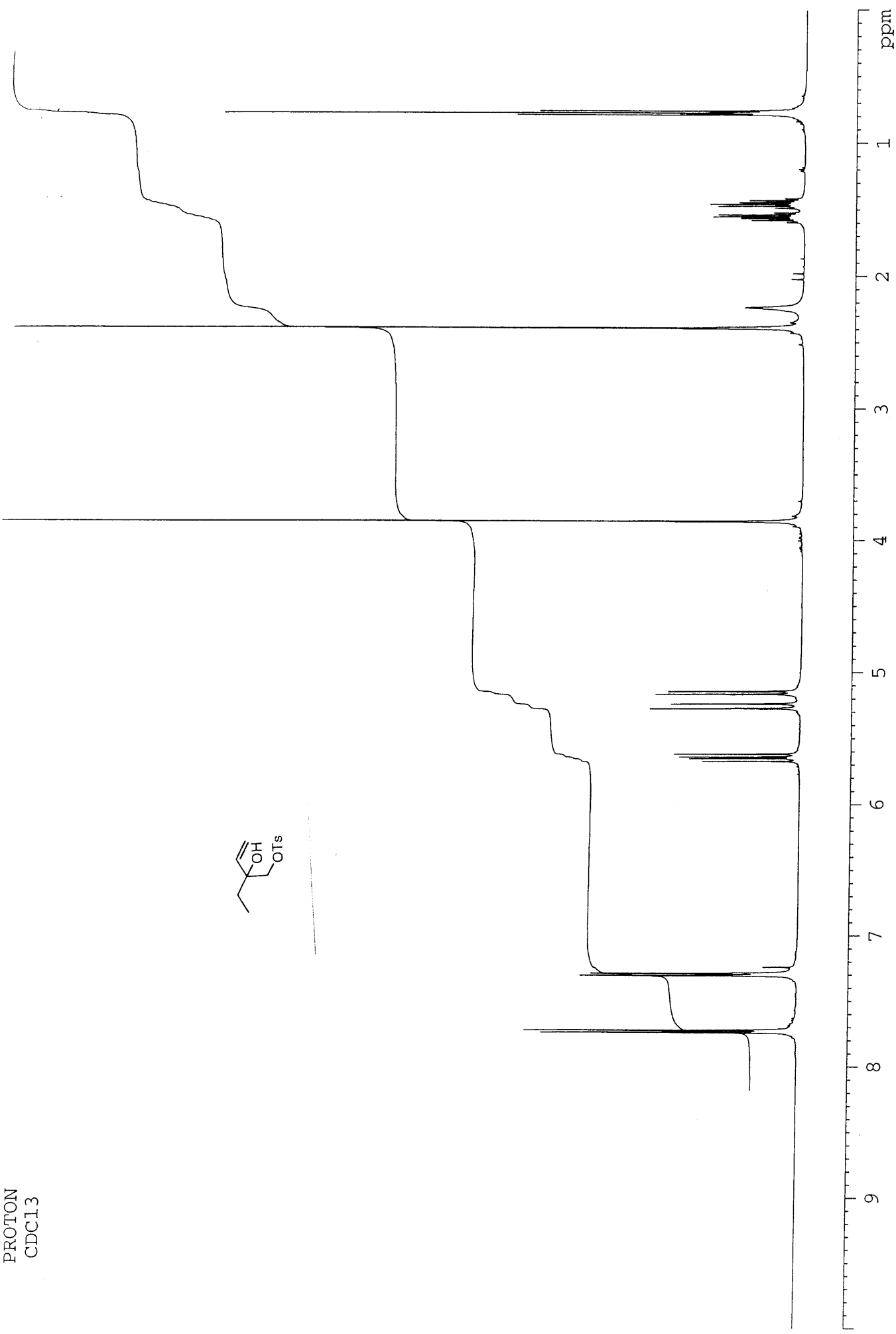
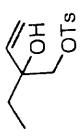




Sample: JG-134  
Instrument Resolution: 7000  
Theoretical Mass: (M+H) 117.09155  
Measured Mass: (M+H) 117.09099  
Error: 4.78 ppm



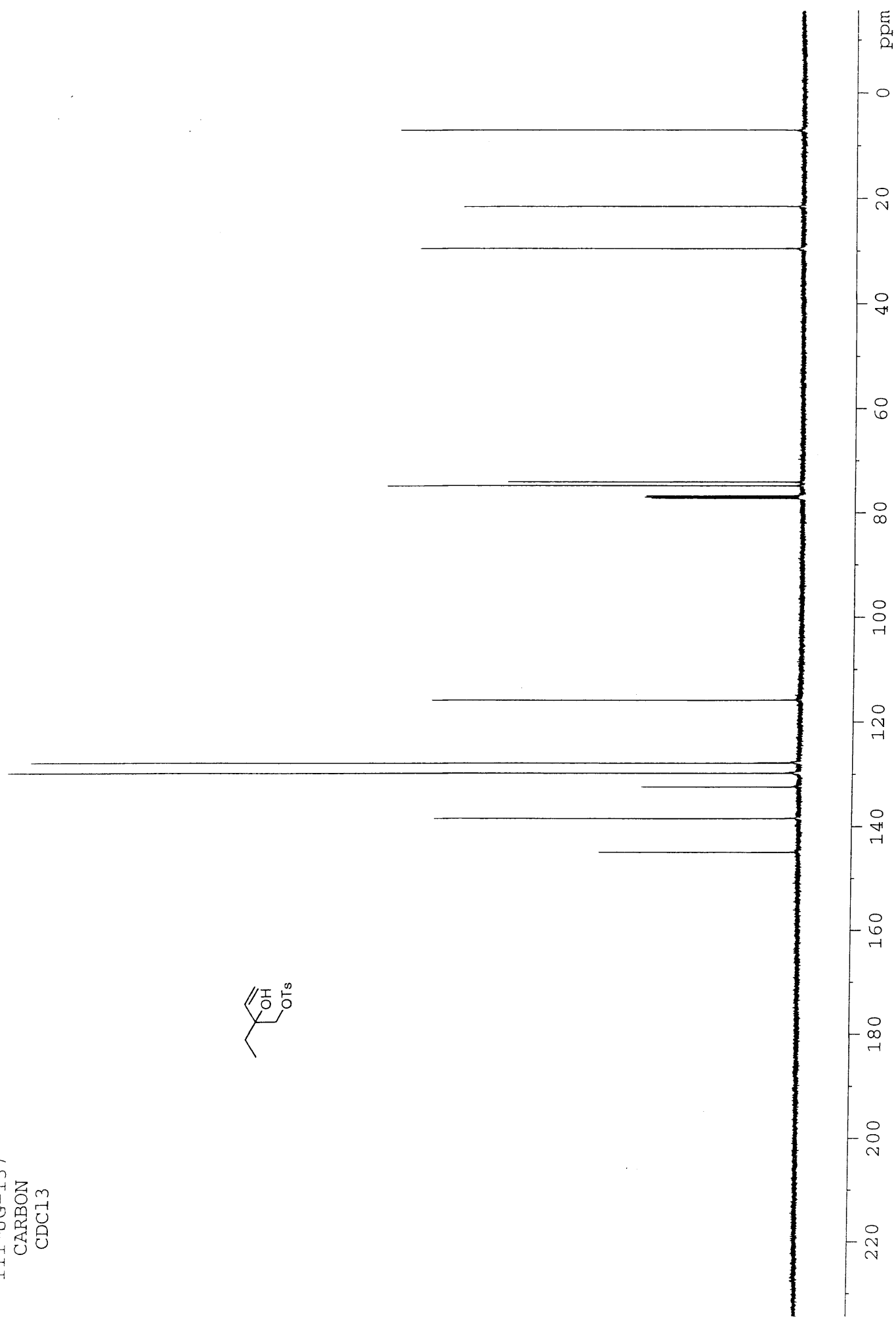
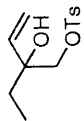
III-JG-137  
PROTON  
CDCl3



III-JG-137

CARBON

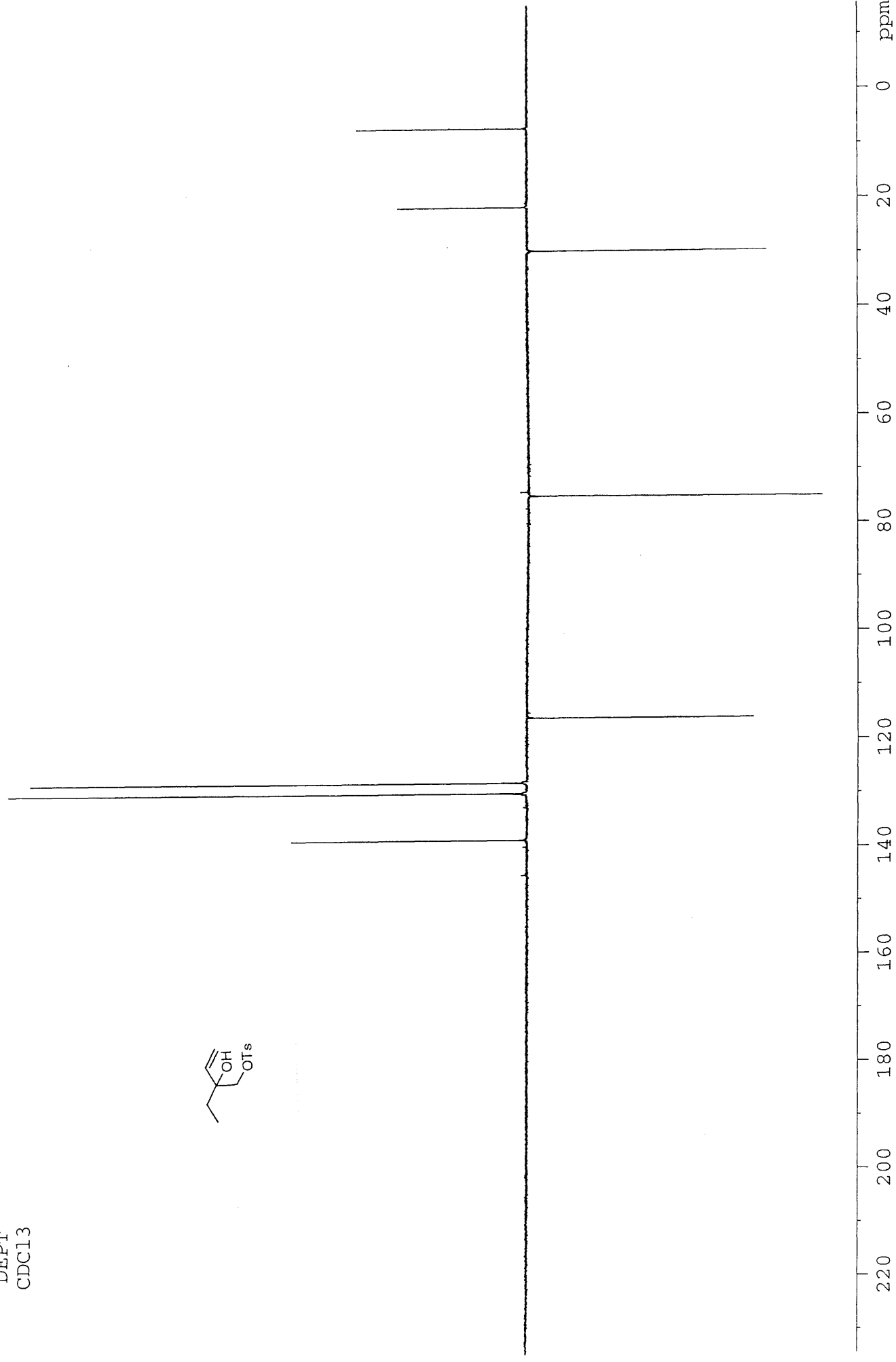
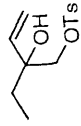
CDCl<sub>3</sub>



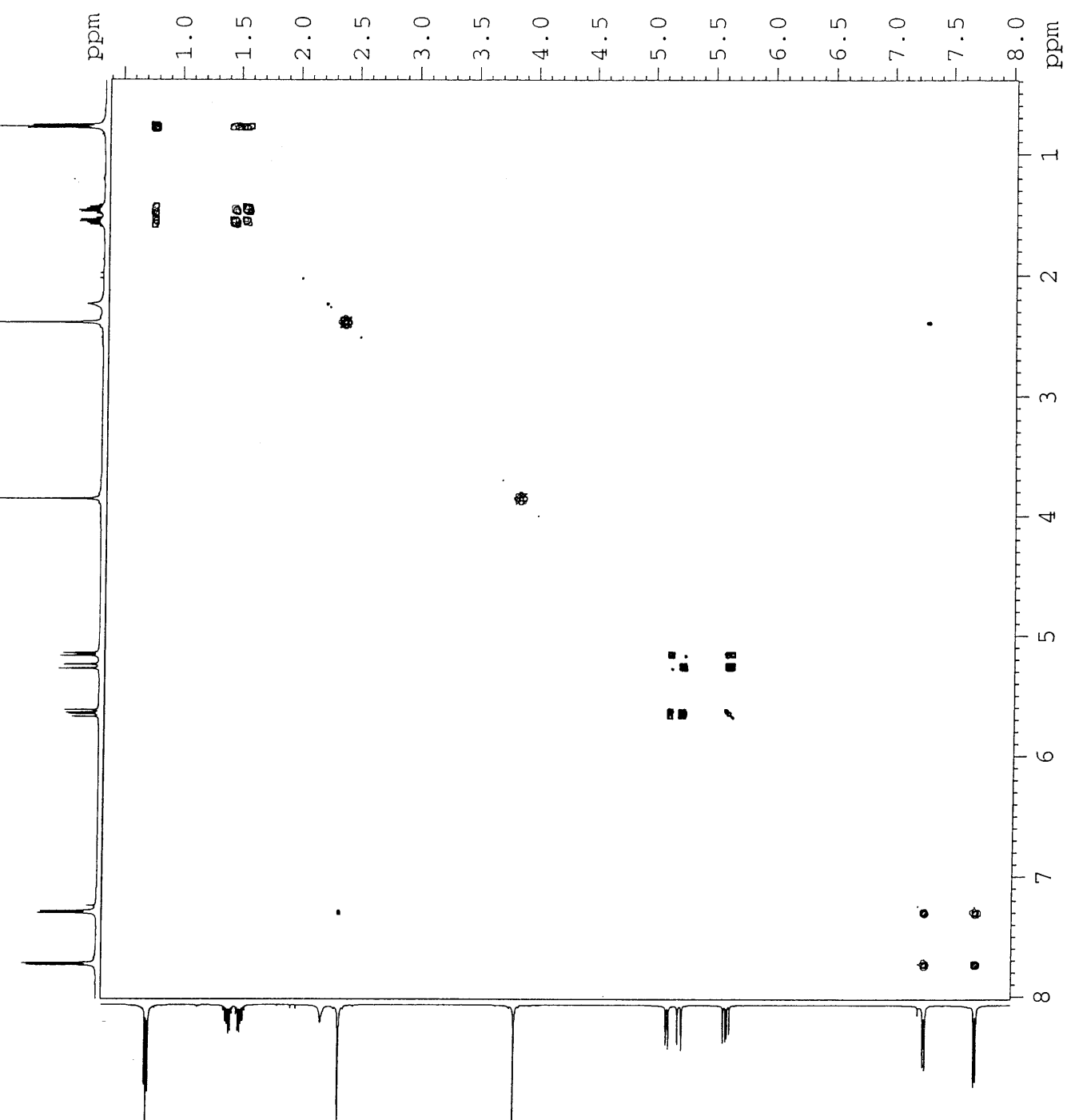
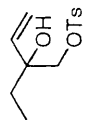
III-JG-137

DEPT

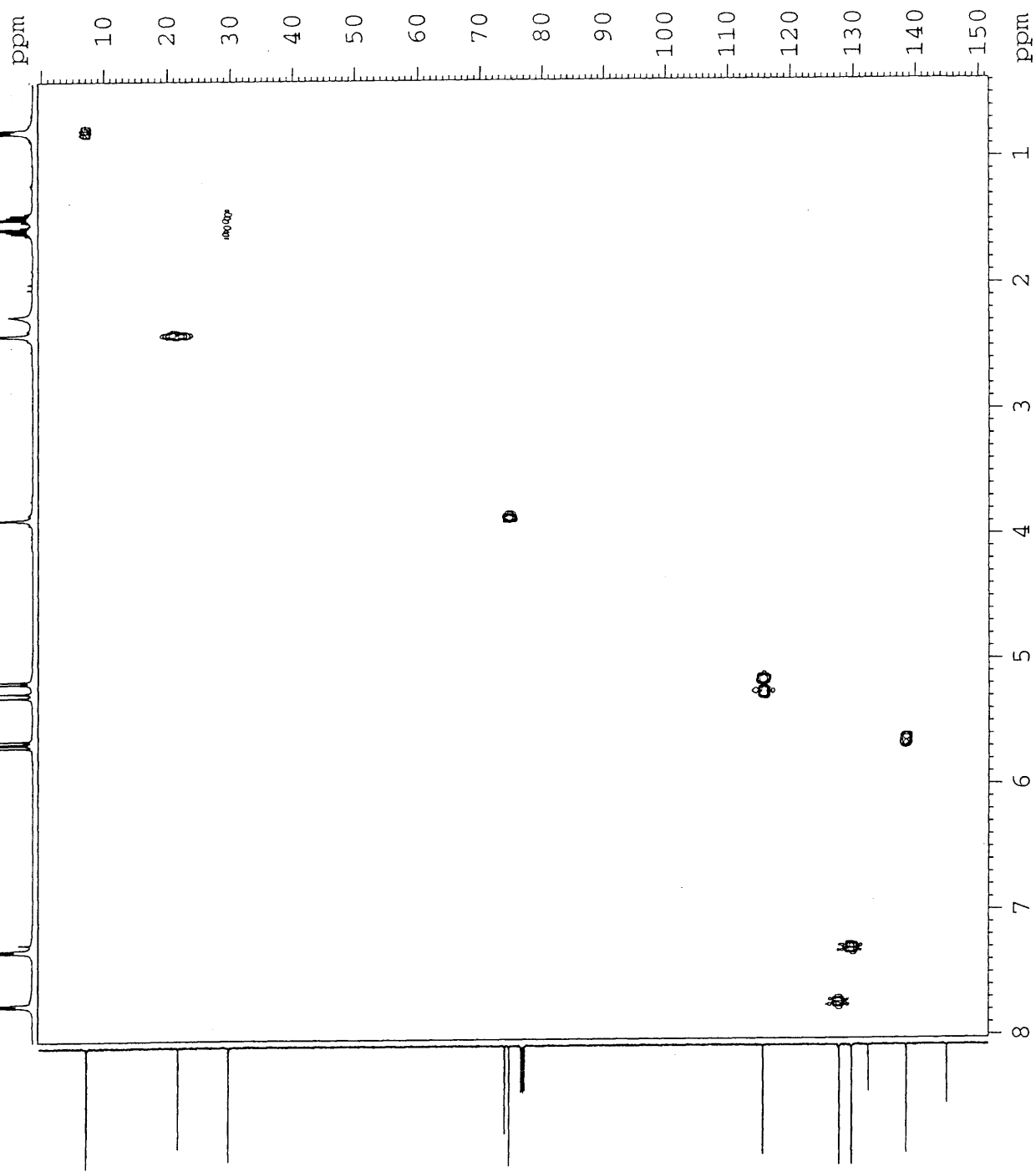
CDC13

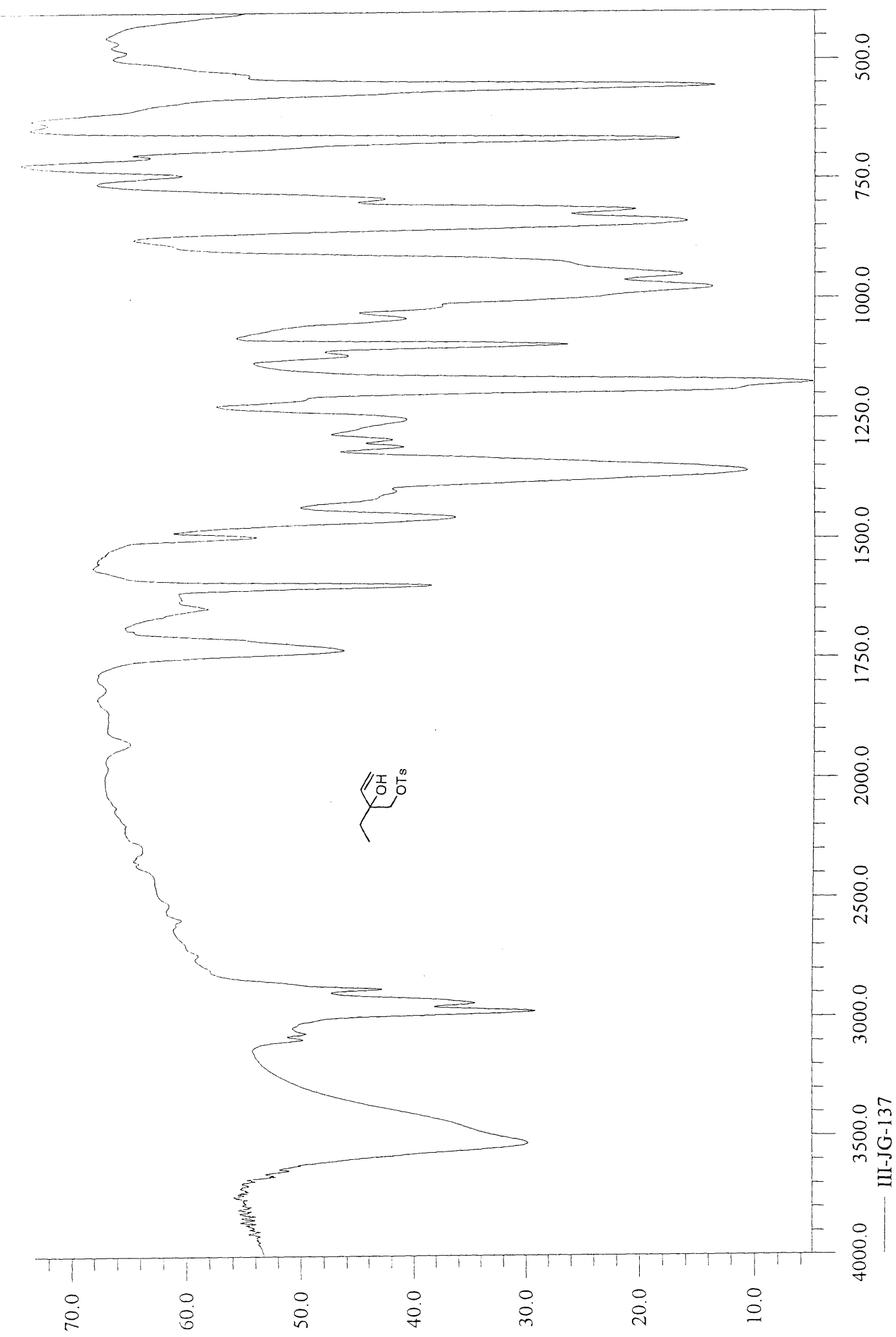


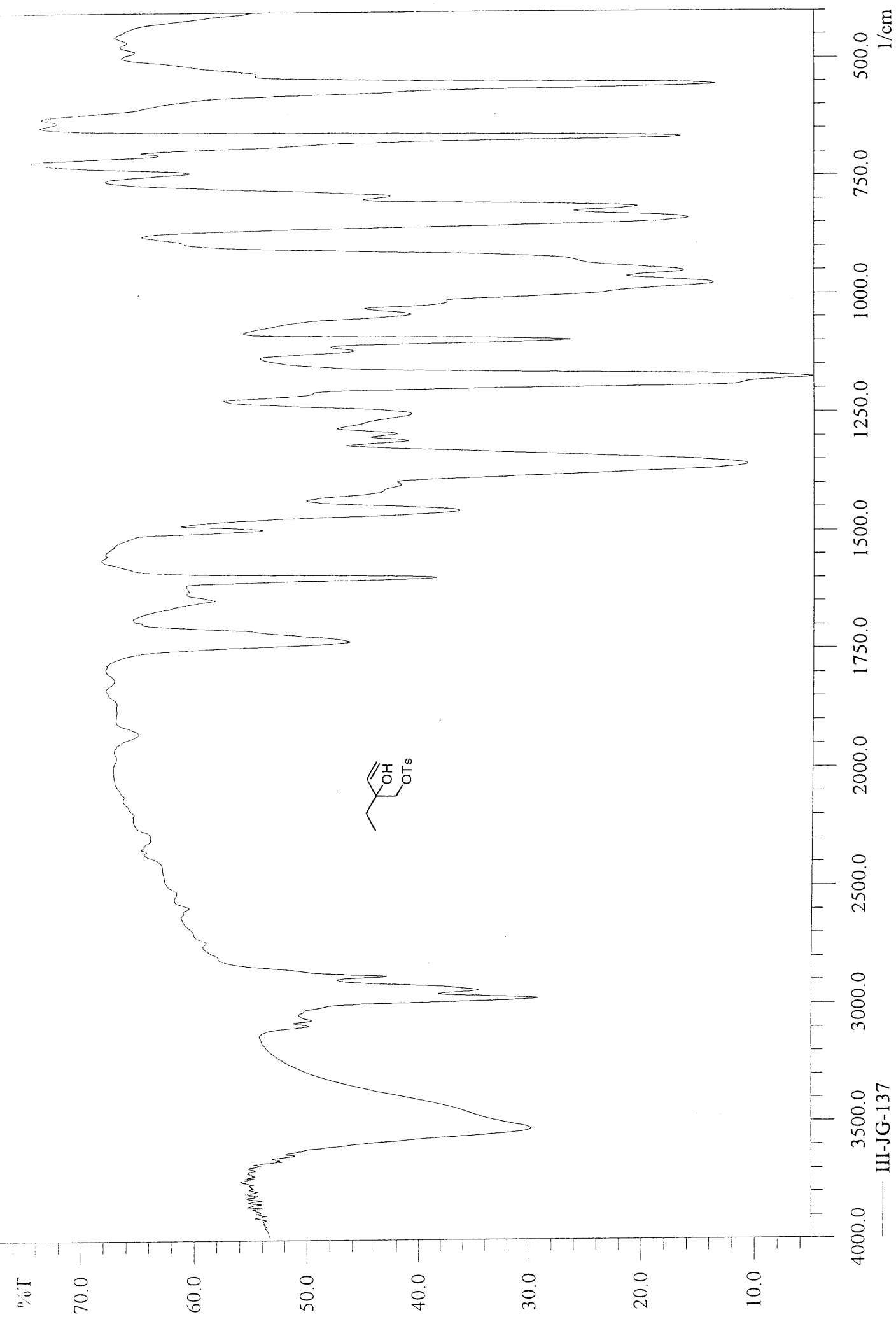
III-JG-137  
COSY  
CDCl<sub>3</sub>



III-JG-137  
HMQC  
CDCl<sub>3</sub>

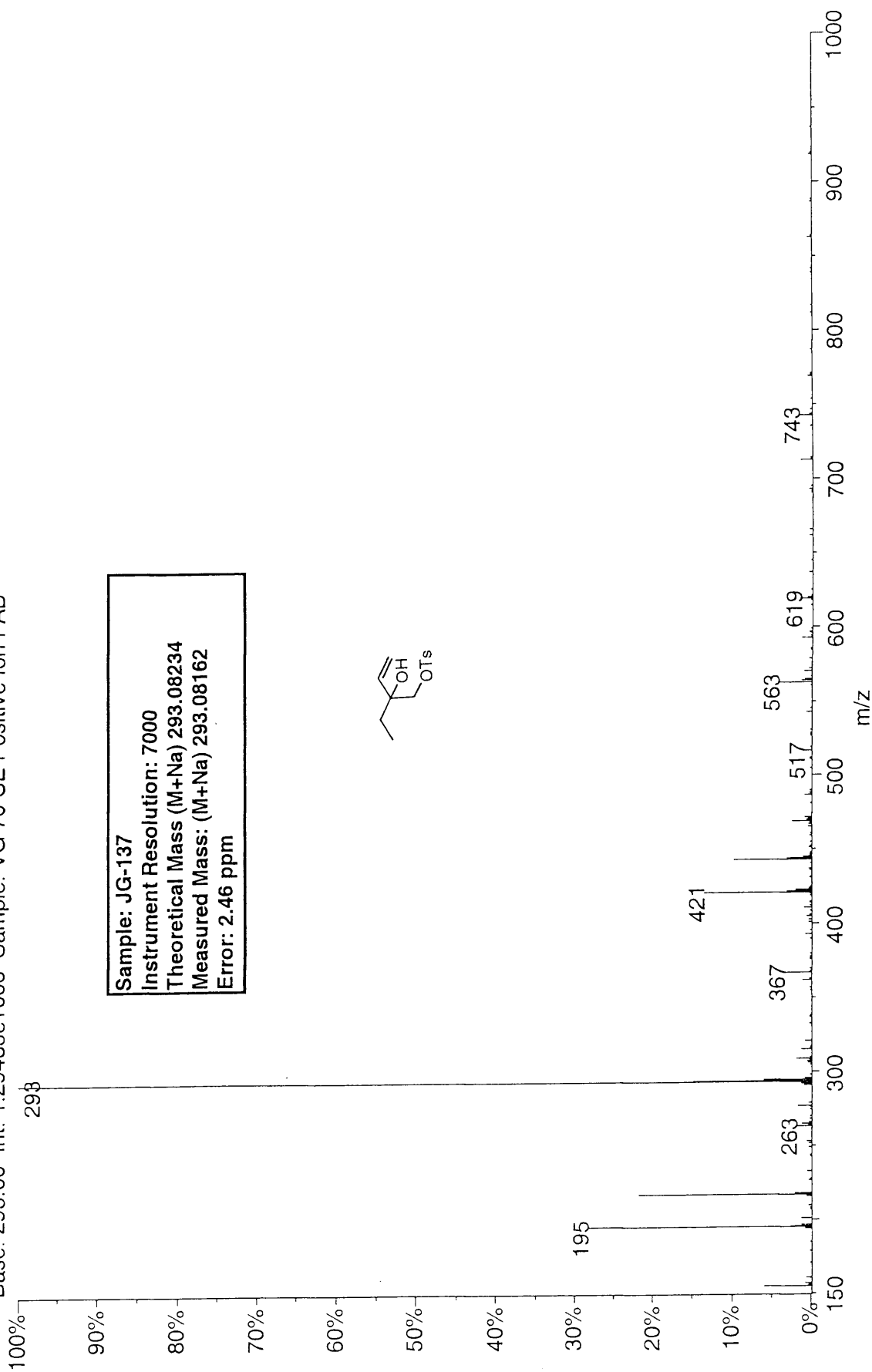




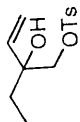




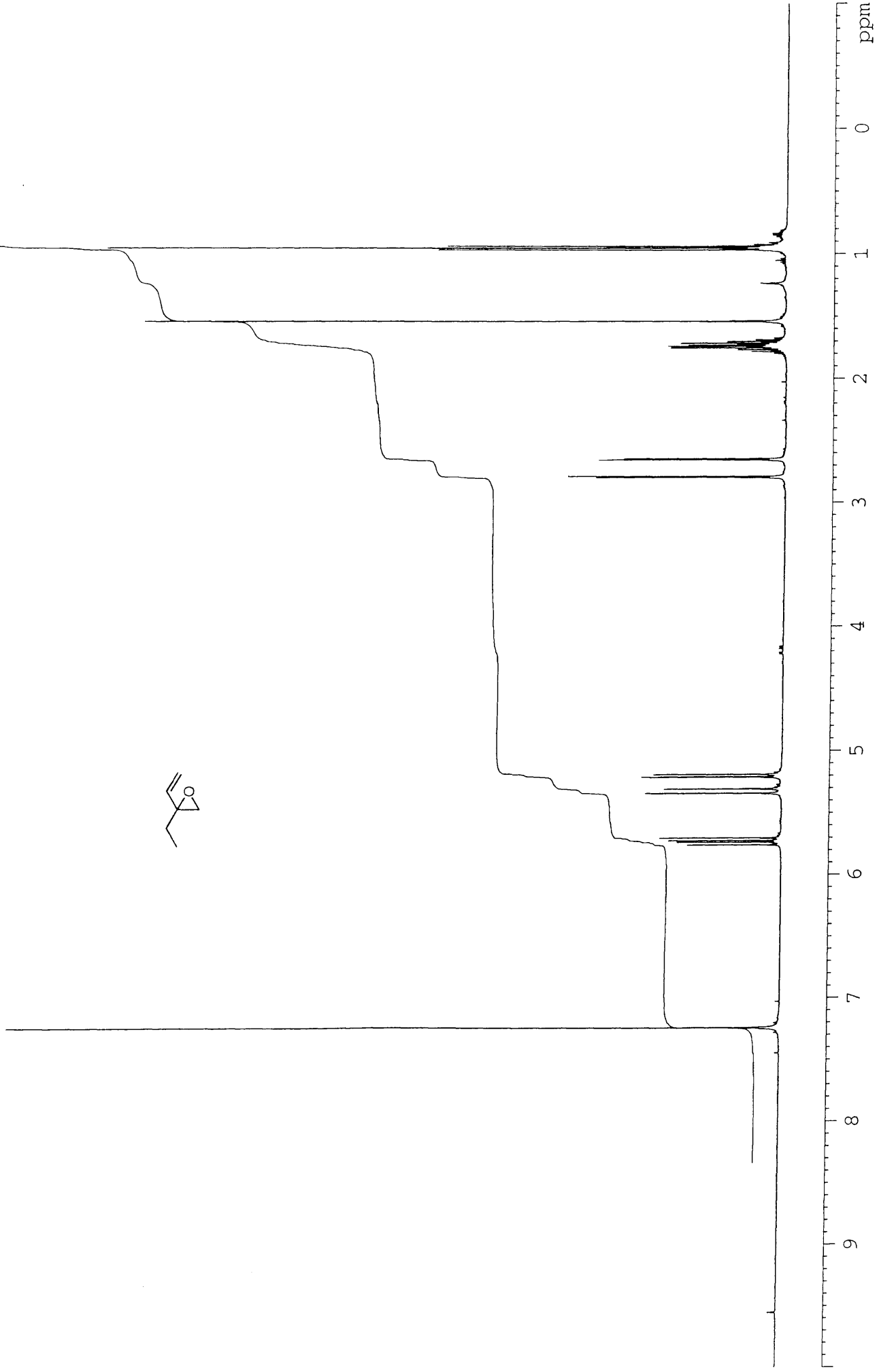
01120506: Scan 177 (32.40 min) - Back  
Base: 293.00 Int: 1.29483e+006 Sample: VG 70-SE Positive Ion FAB



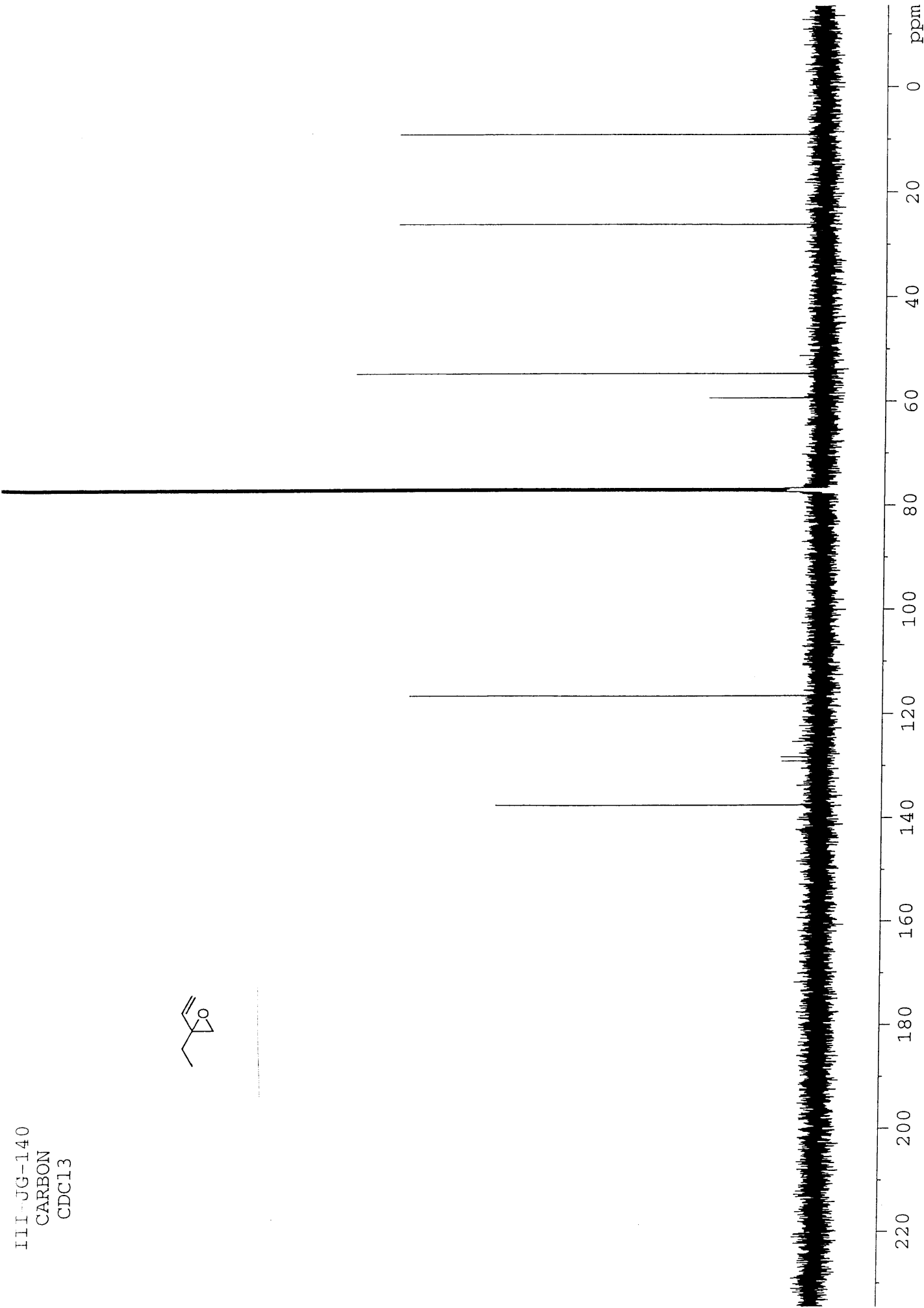
Sample: JG-137  
Instrument Resolution: 7000  
Theoretical Mass (M+Na) 293.08234  
Measured Mass: (M+Na) 293.08162  
Error: 2.46 ppm



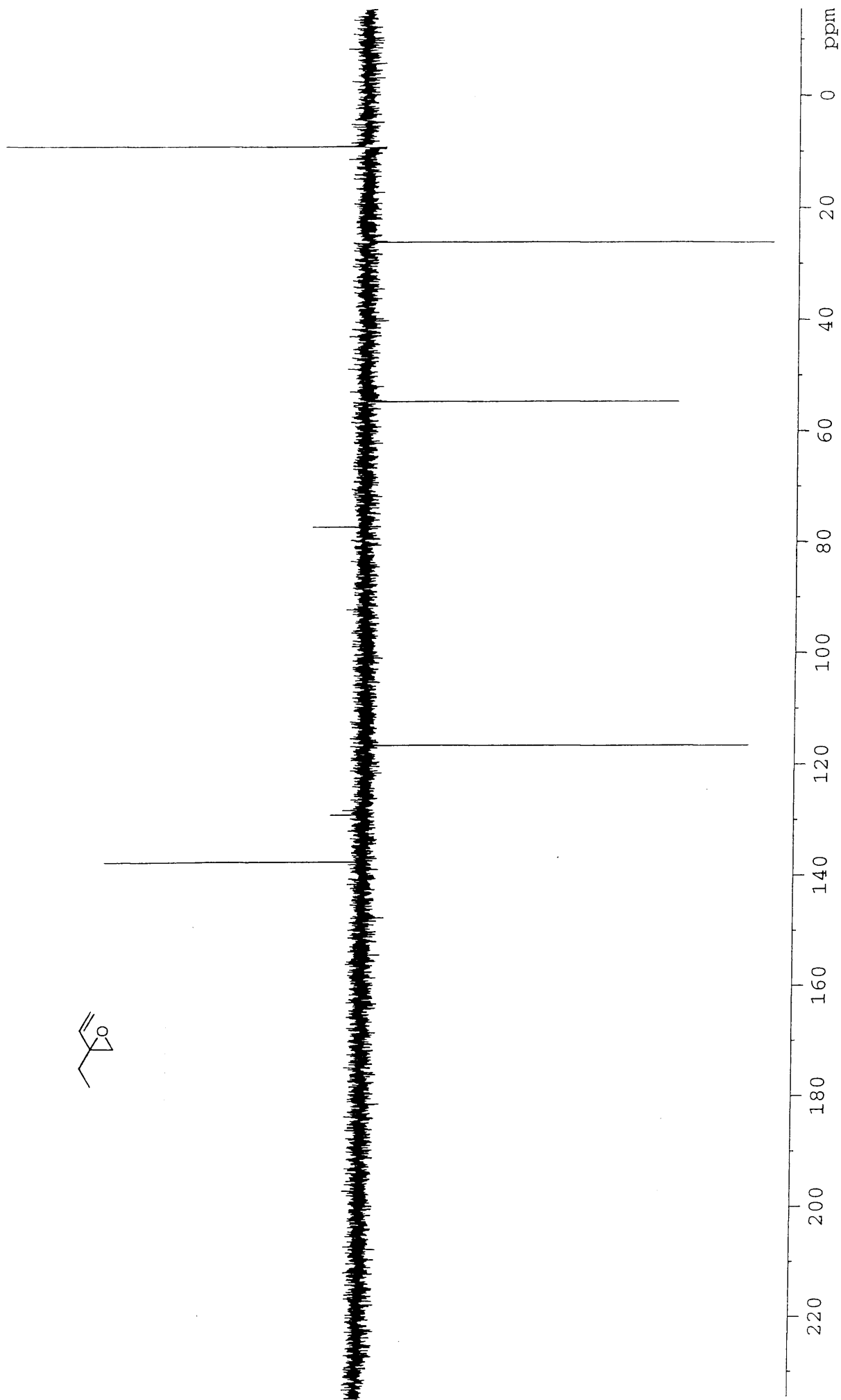
III-JG-140  
PROTON  
CDCl3



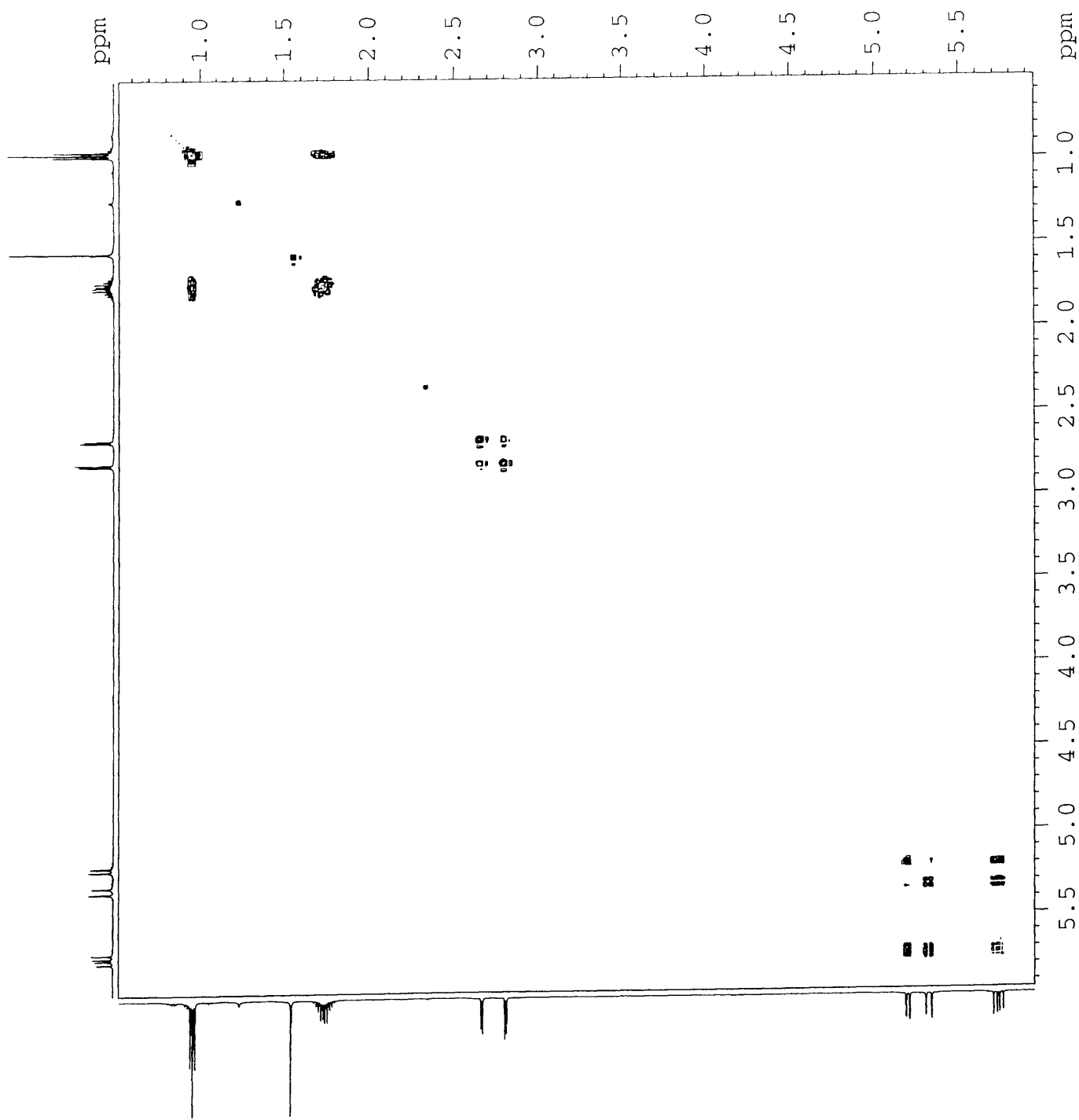
III-JG-140  
CARBON  
CDCl<sub>3</sub>



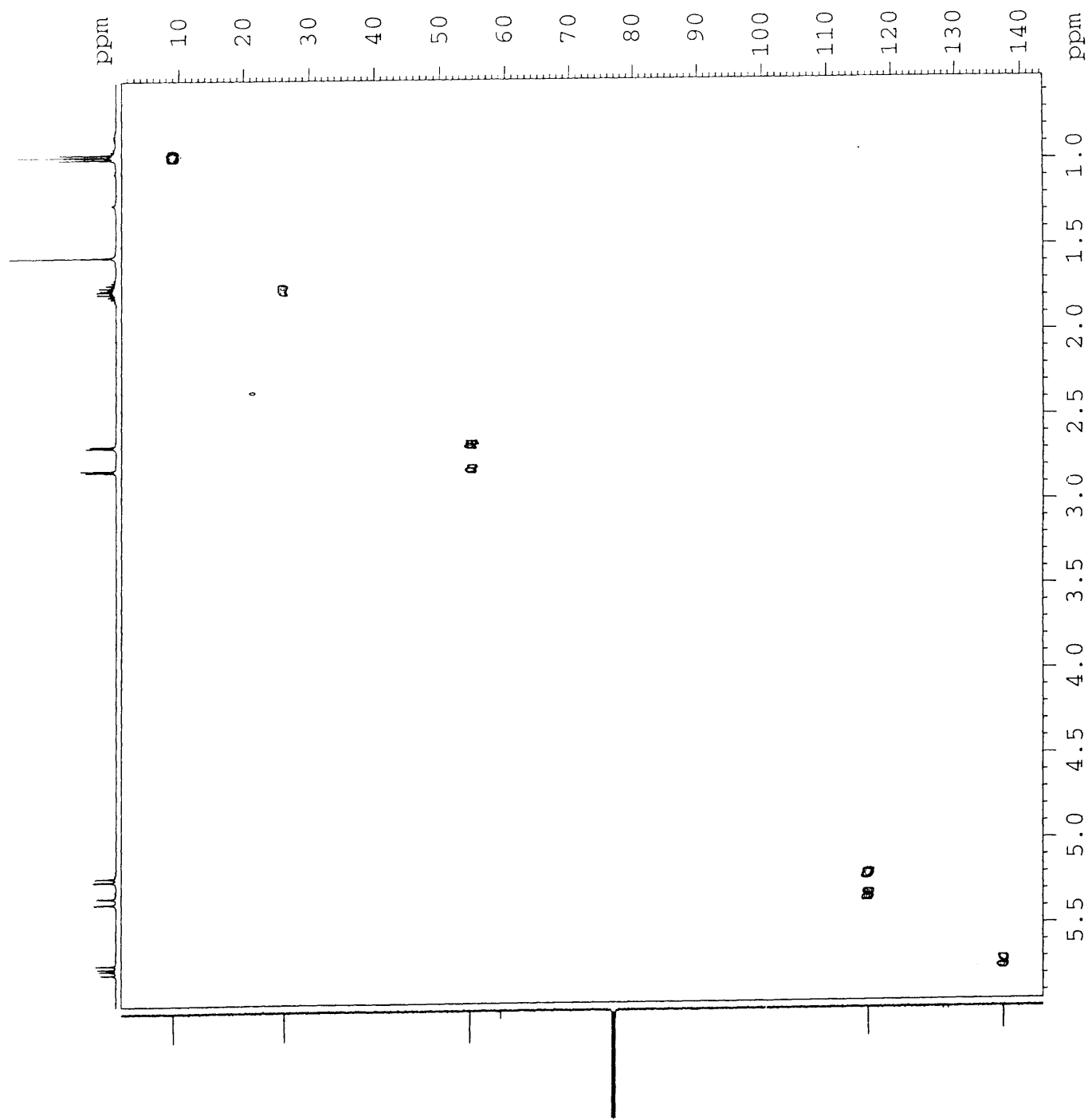
III-JG-140  
DEPT  
CDCl<sub>3</sub>



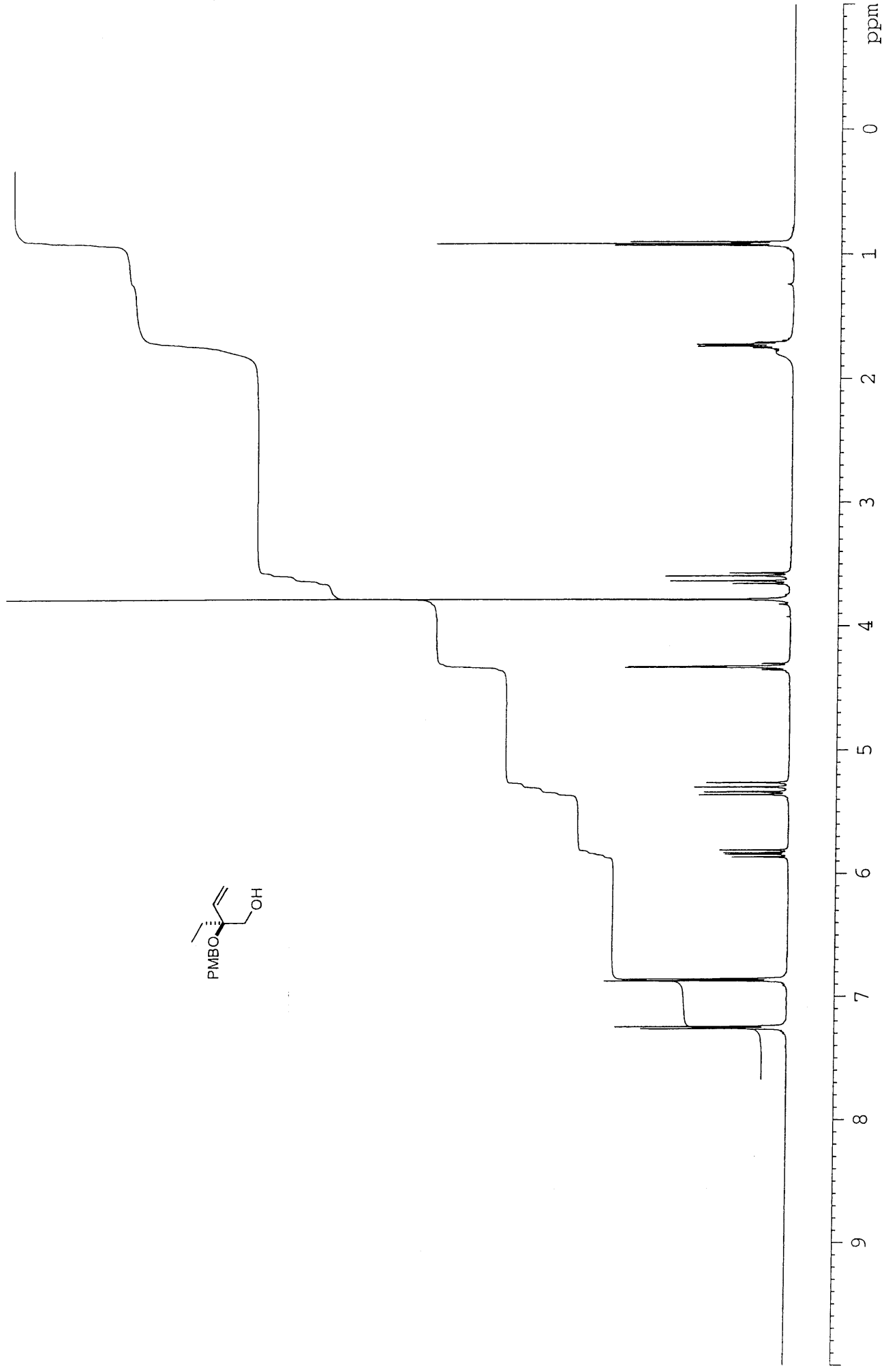
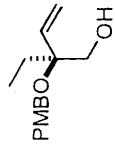
111-JG-140  
COSY  
CDCl<sub>3</sub>



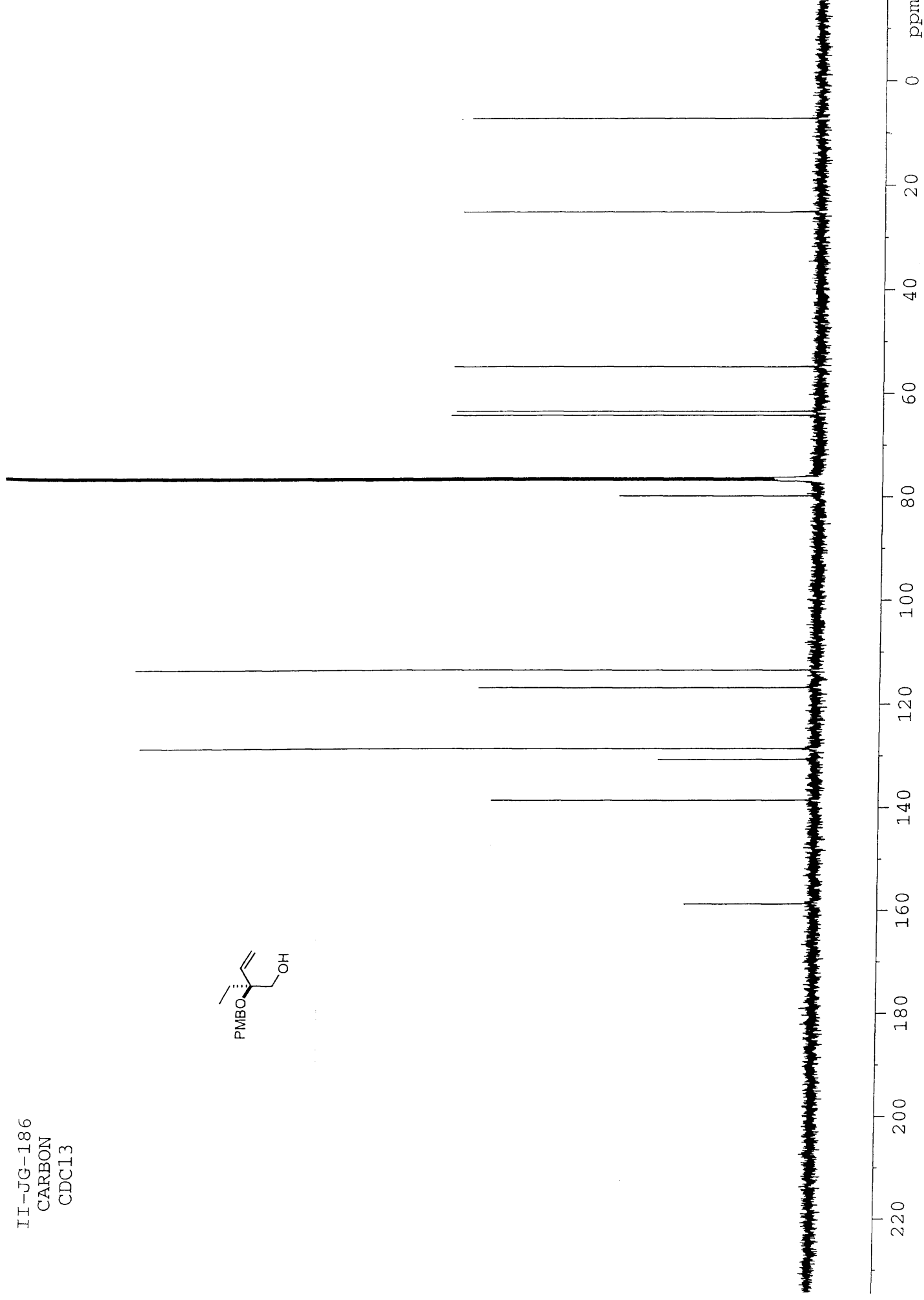
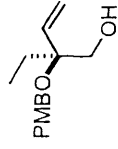
2017-06-14  
HMOC  
CDCl3



II-JG-186  
PROTON  
CDCl3

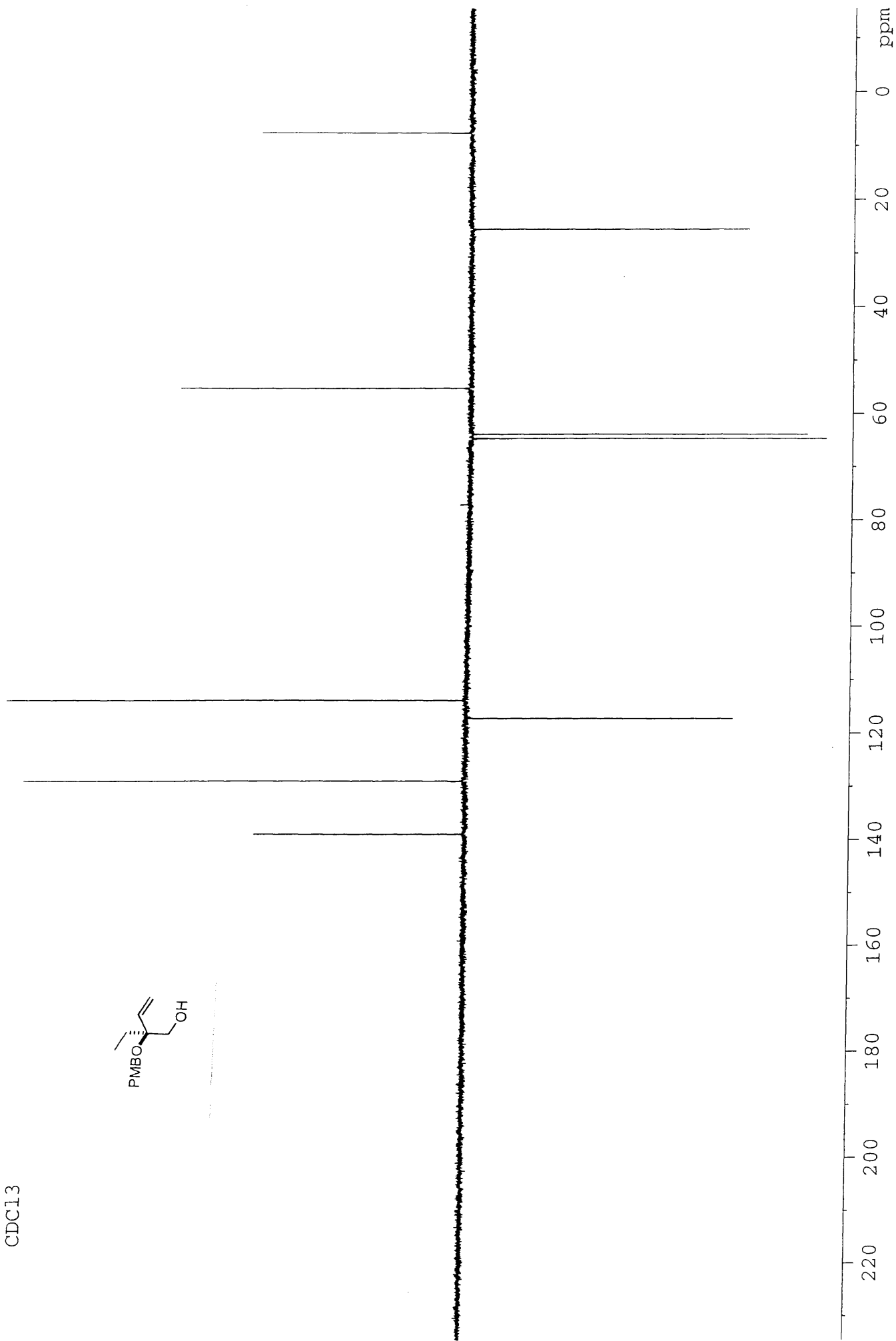
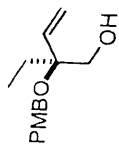


II-JG-186  
CARBON  
CDCl<sub>3</sub>

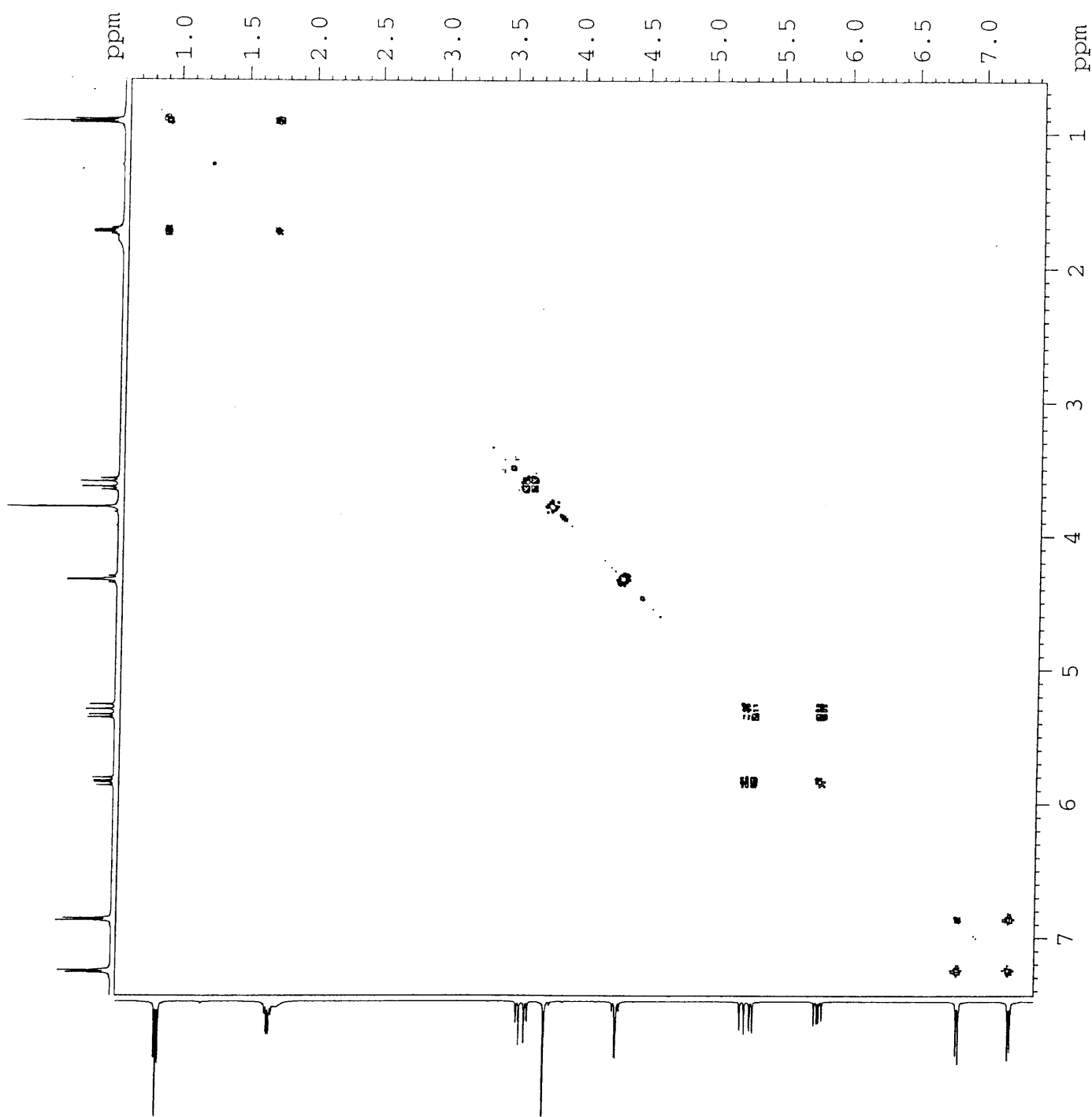
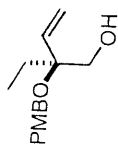




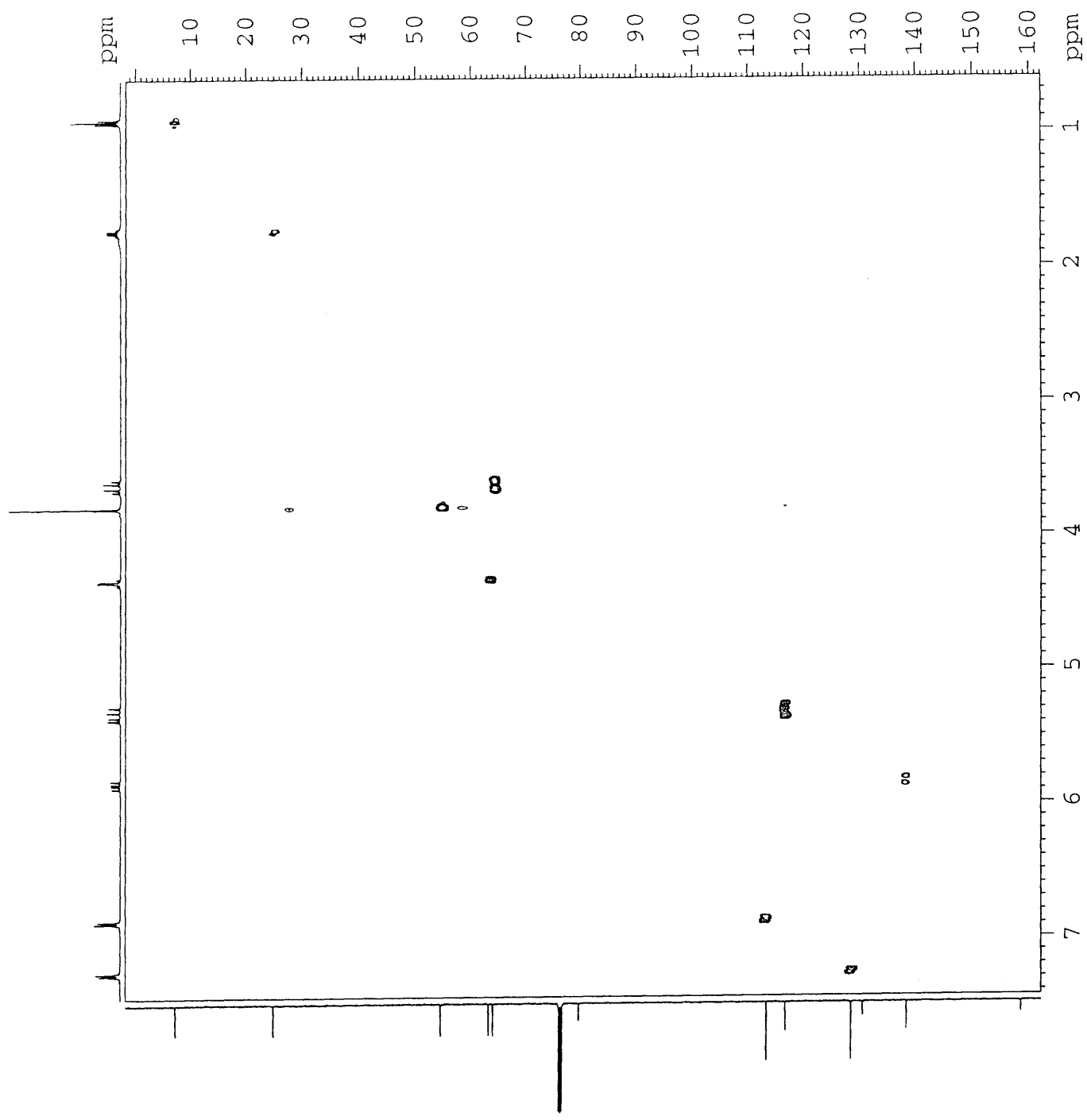
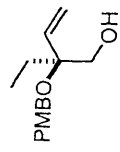
II-JG-186  
DEPT  
CDC13

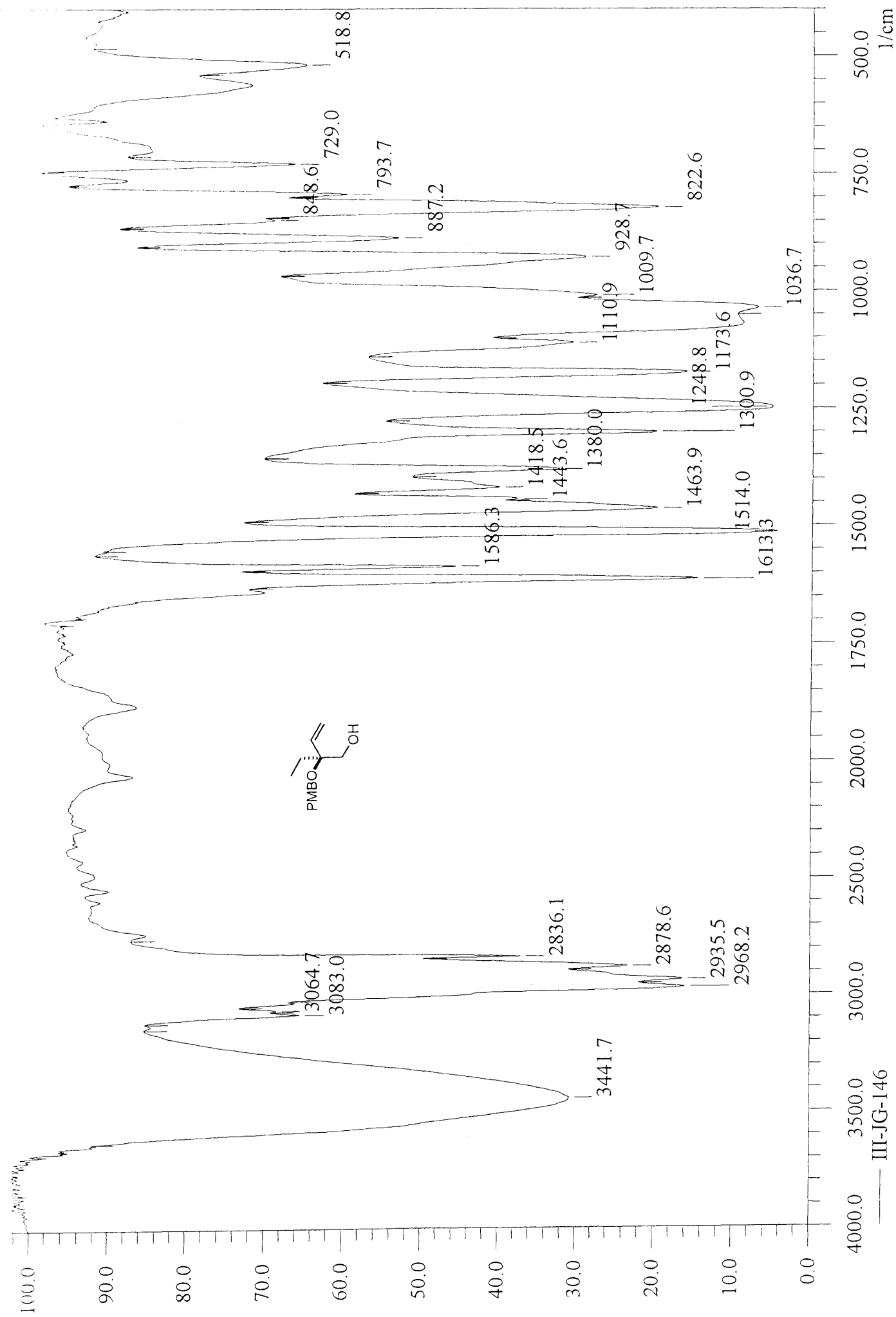


II-JG-186  
COSY  
CDCl<sub>3</sub>

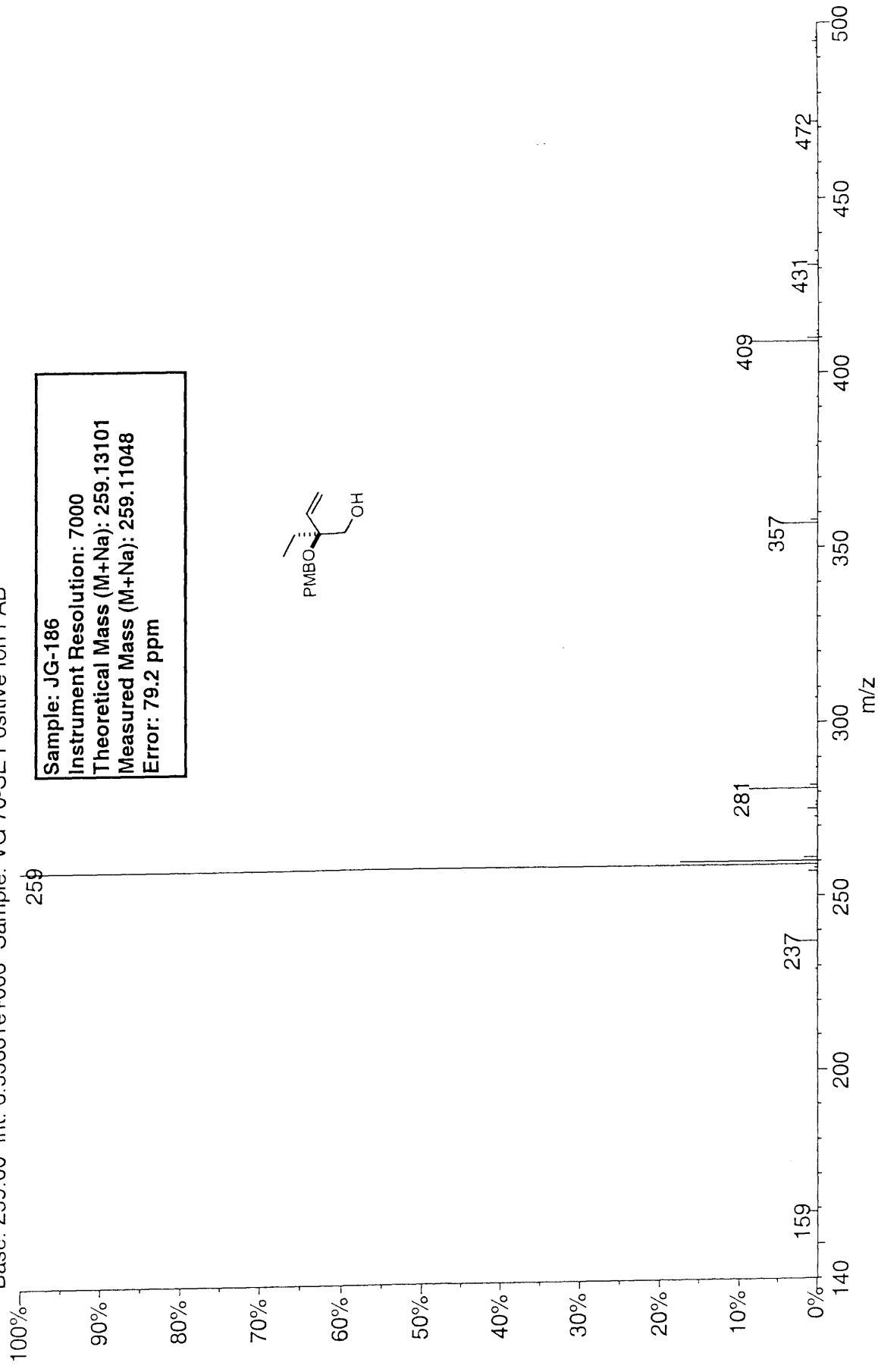


II-JG-186  
HMQC  
CDCl<sub>3</sub>

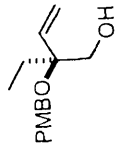




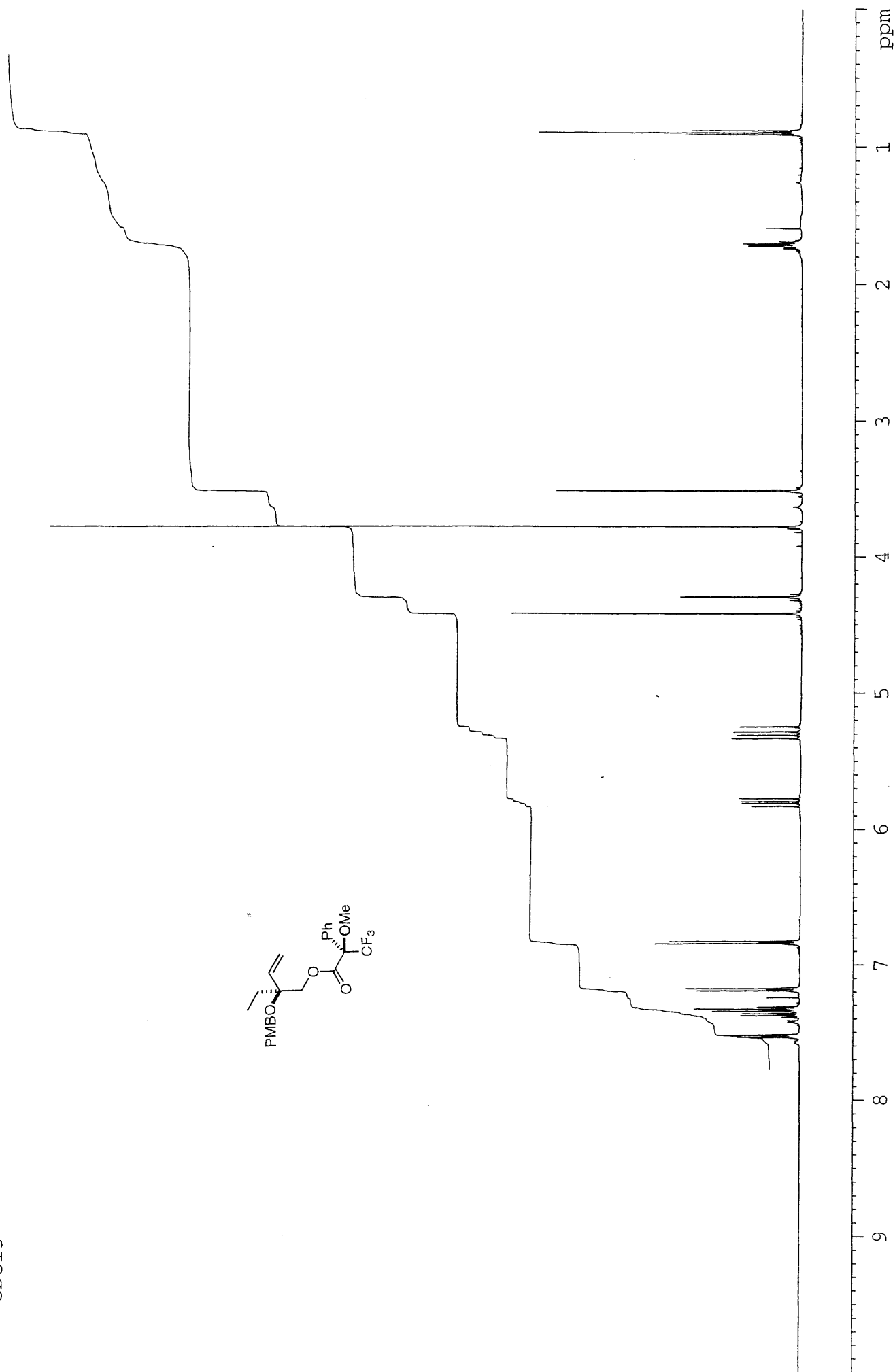
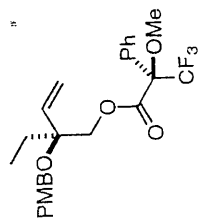
02170706: Scan 187 (37.30 min) - Back  
Base: 259.00 Int: 6.53681e+006 Sample: VG 70-SE Positive Ion FAB



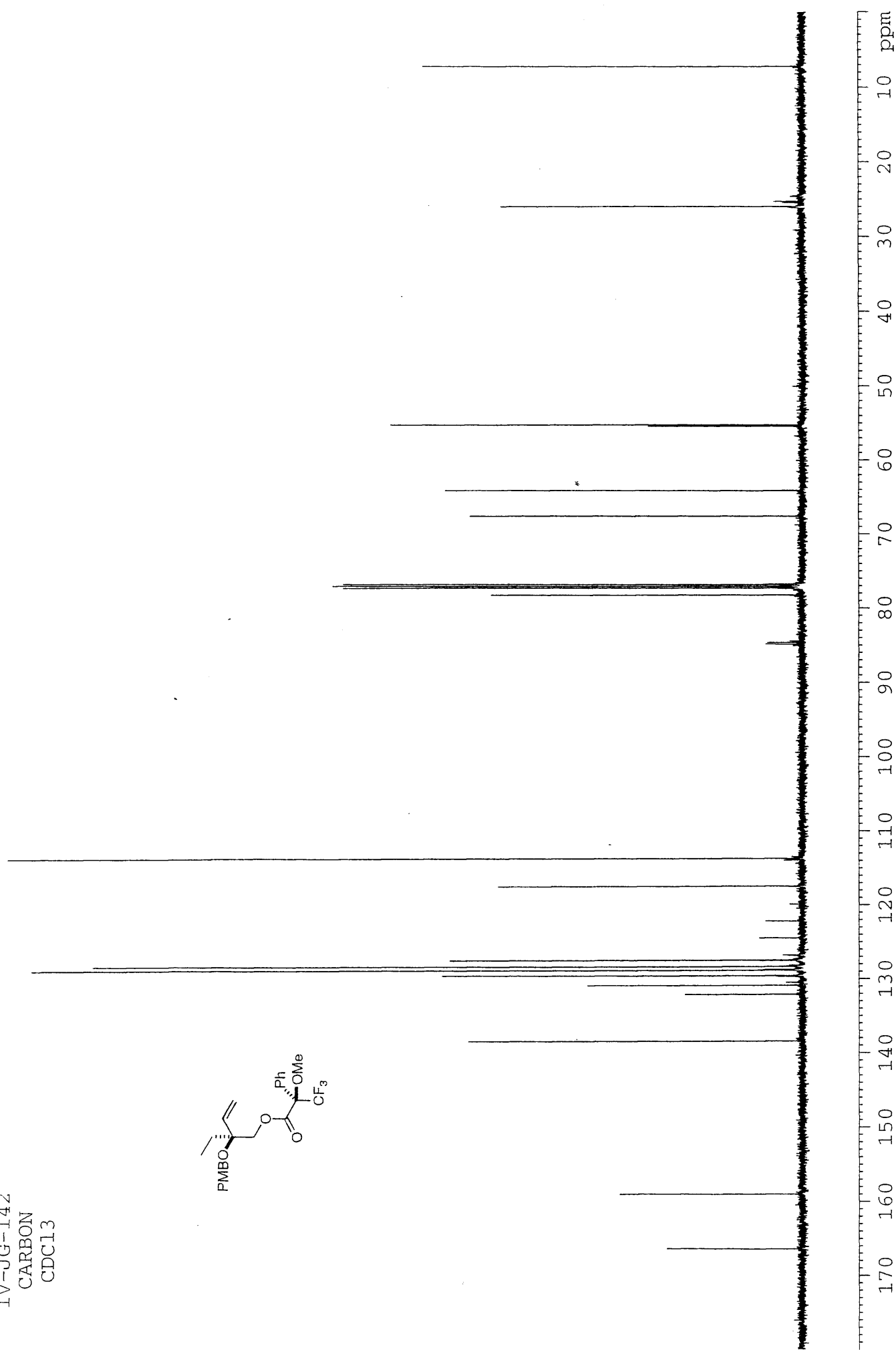
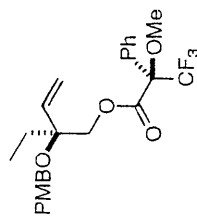
Sample: JG-186  
Instrument Resolution: 7000  
Theoretical Mass (M+Na): 259.13101  
Measured Mass (M+Na): 259.11048  
Error: 79.2 ppm



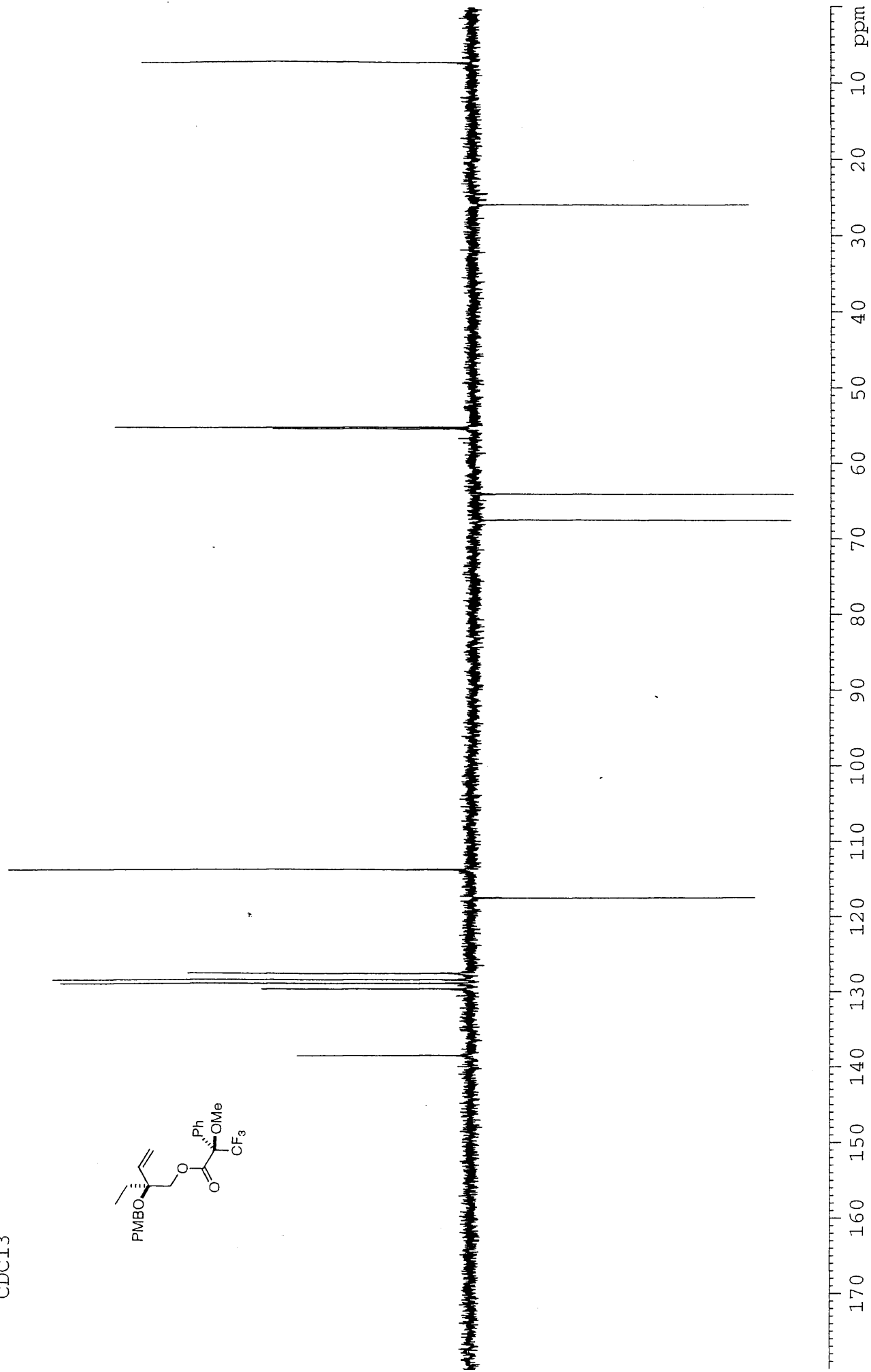
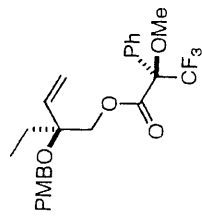
IV-JG-142  
PROTON  
CDCl<sub>3</sub>



IV-JG-142  
CARBON  
CDCl<sub>3</sub>

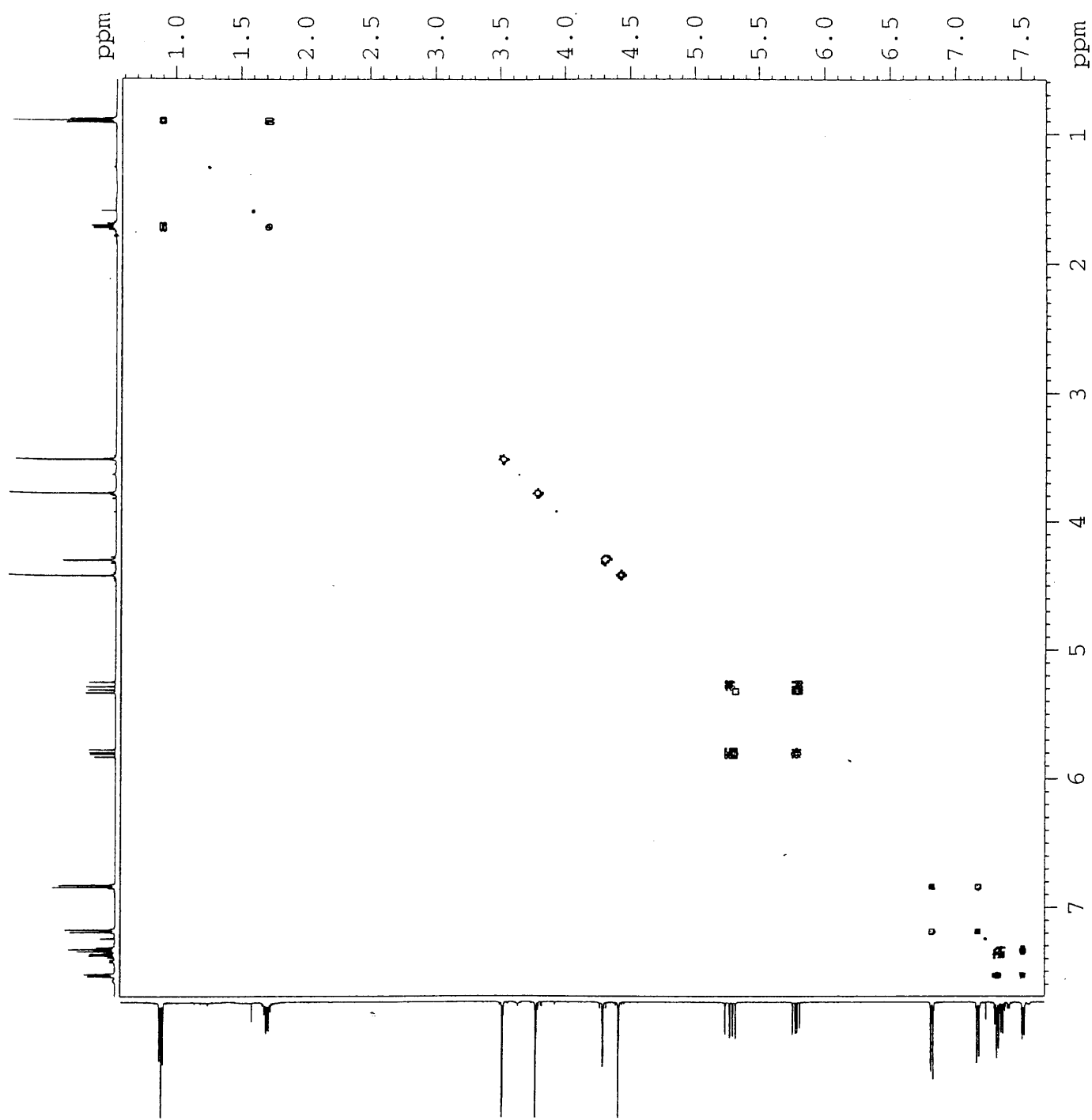
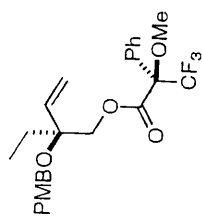


IV-JG-142  
DEPT  
CDC13

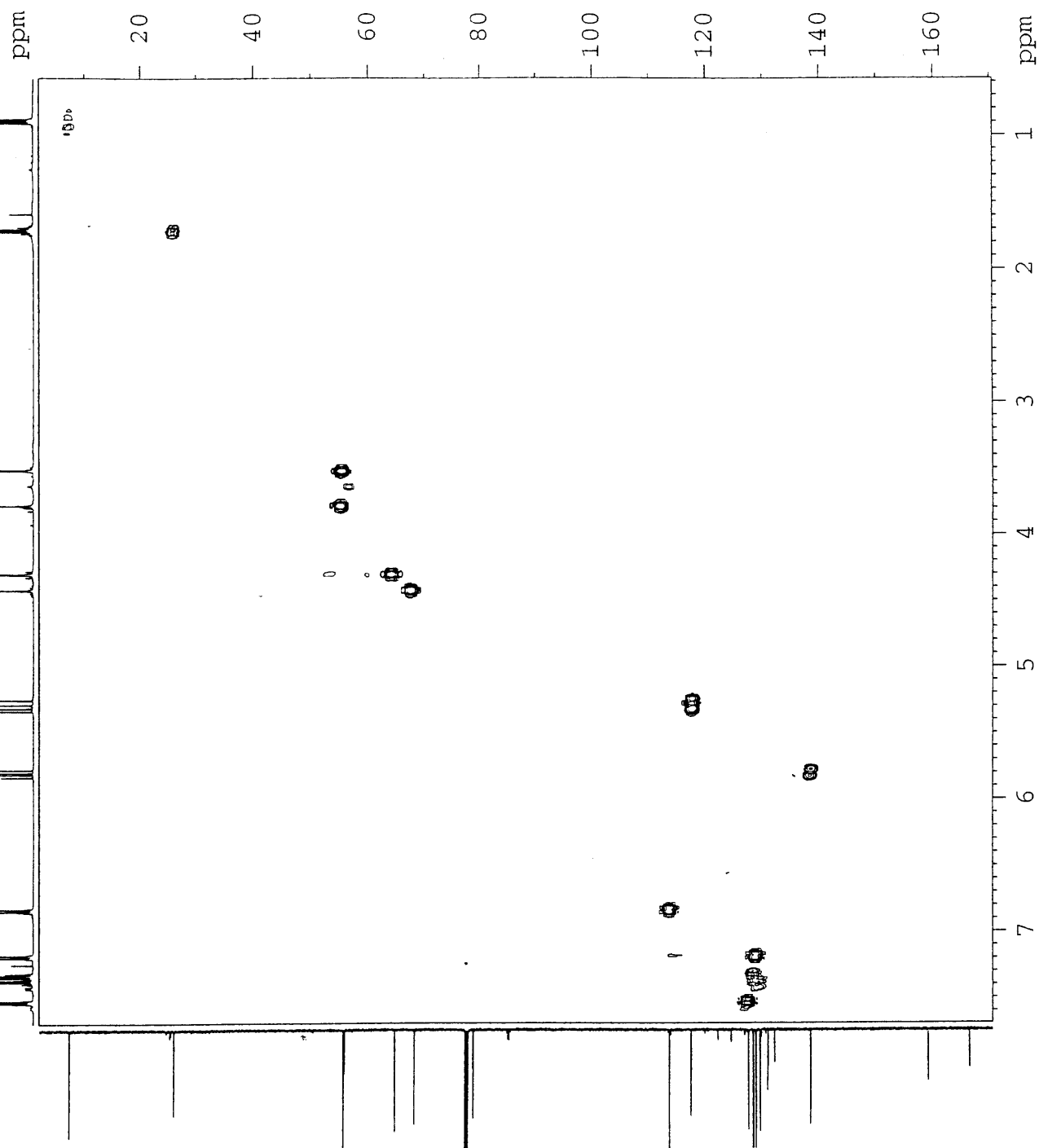
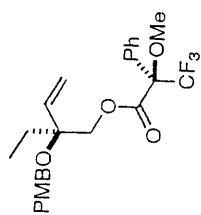




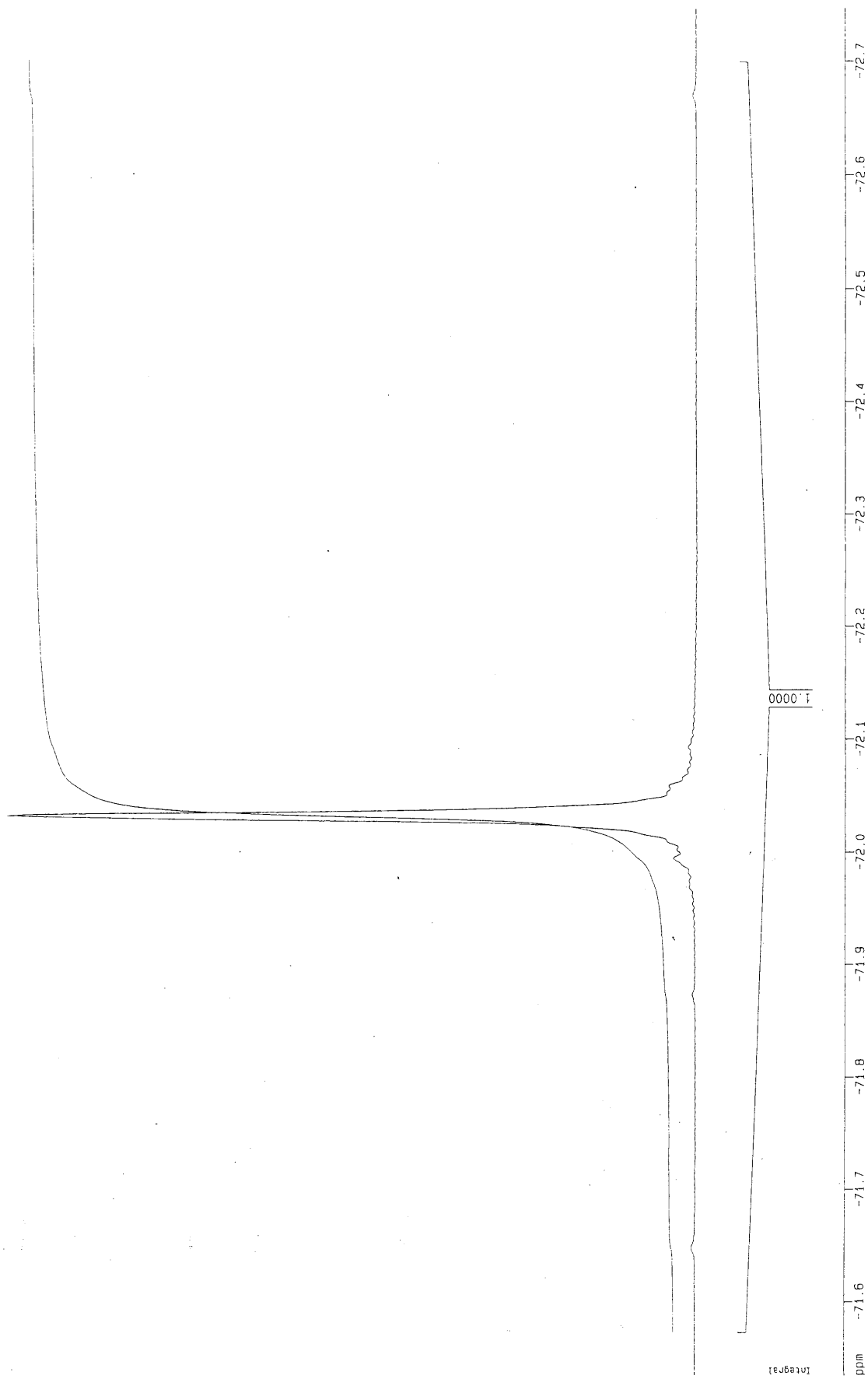
IV-JG-142  
COSY  
CDC13



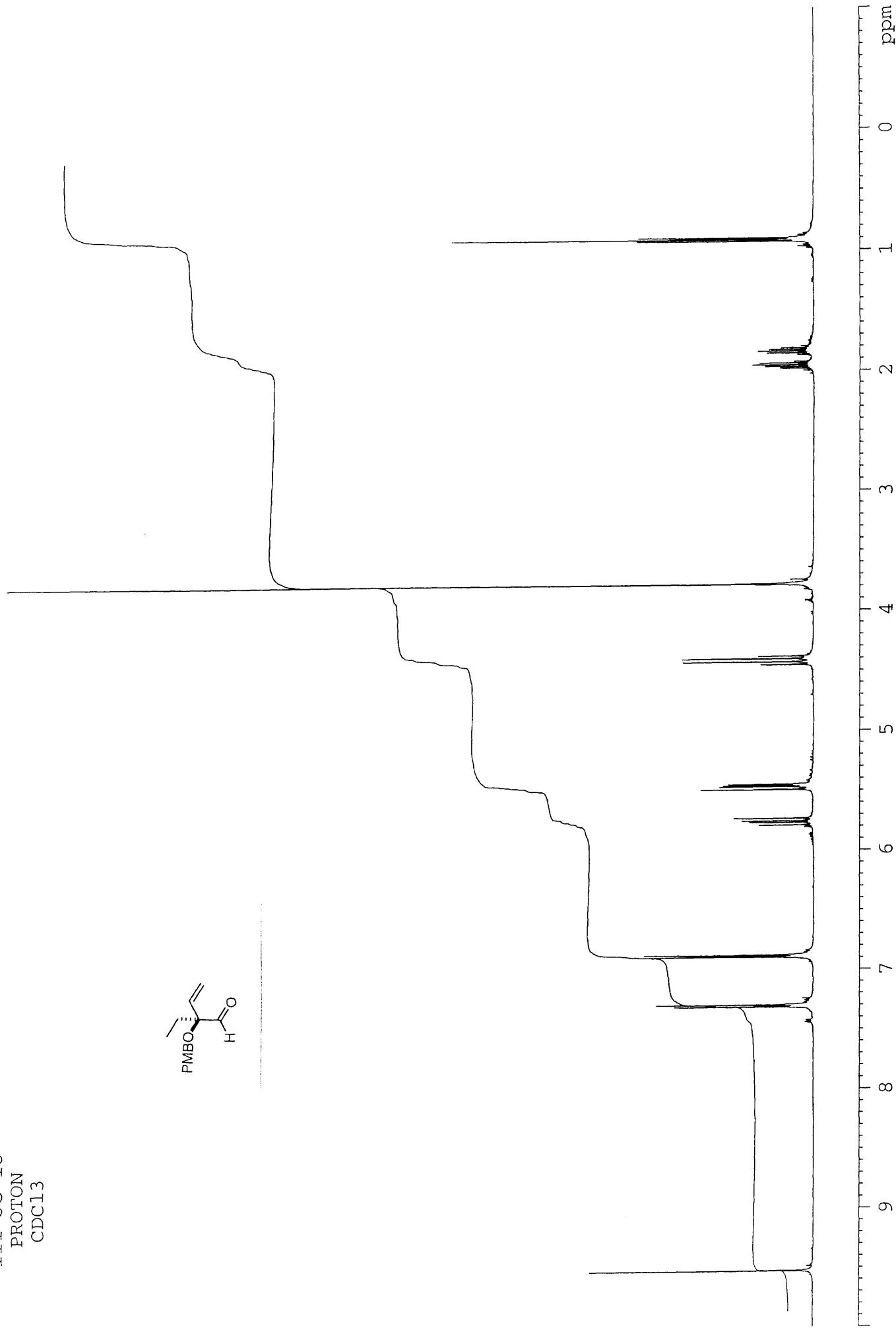
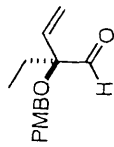
IV-JG-142  
HMQC  
CDCl<sub>3</sub>



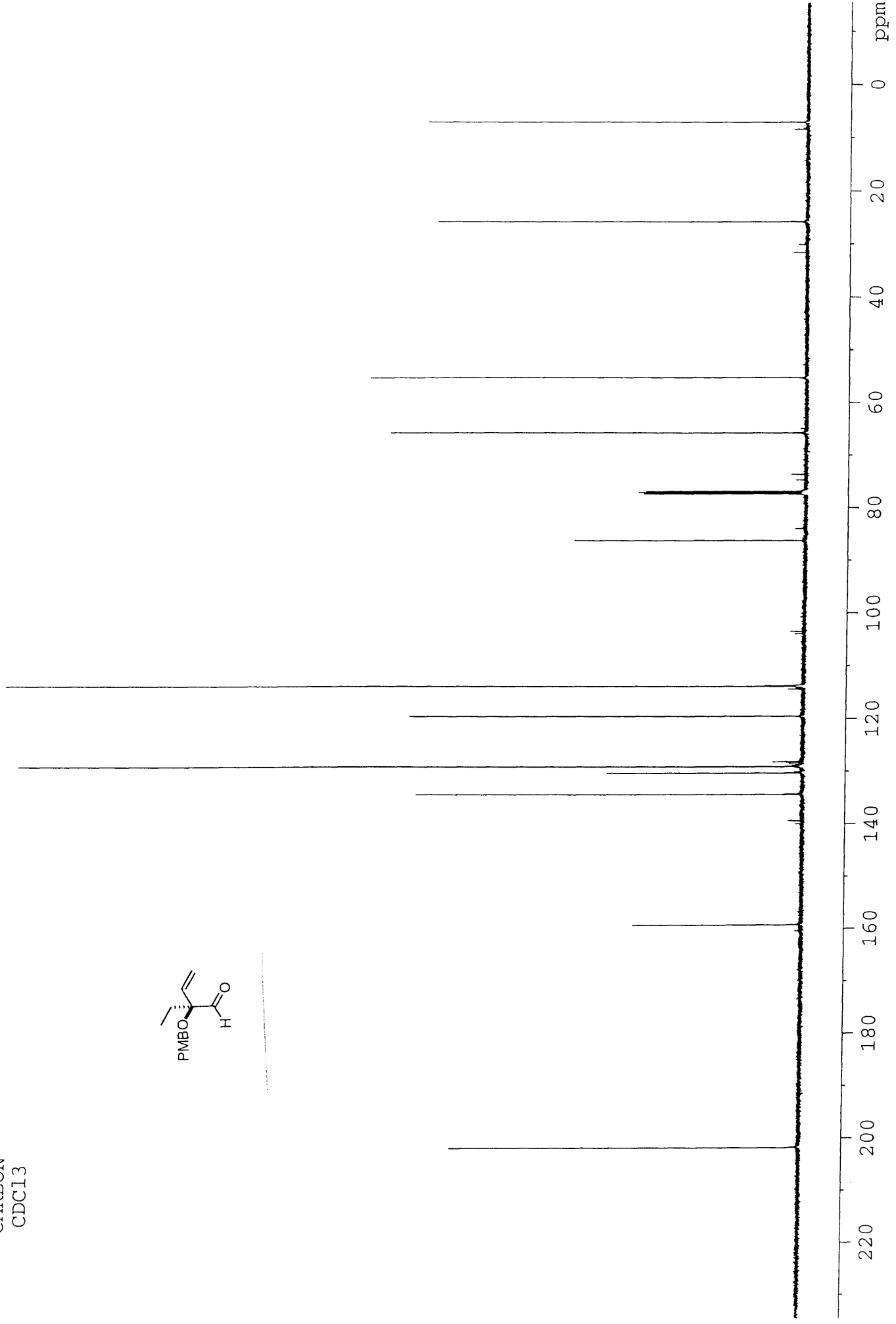
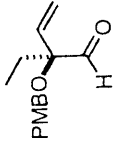
IV-JG-142  
f19cpd.ucl CDC13 v kjh 35



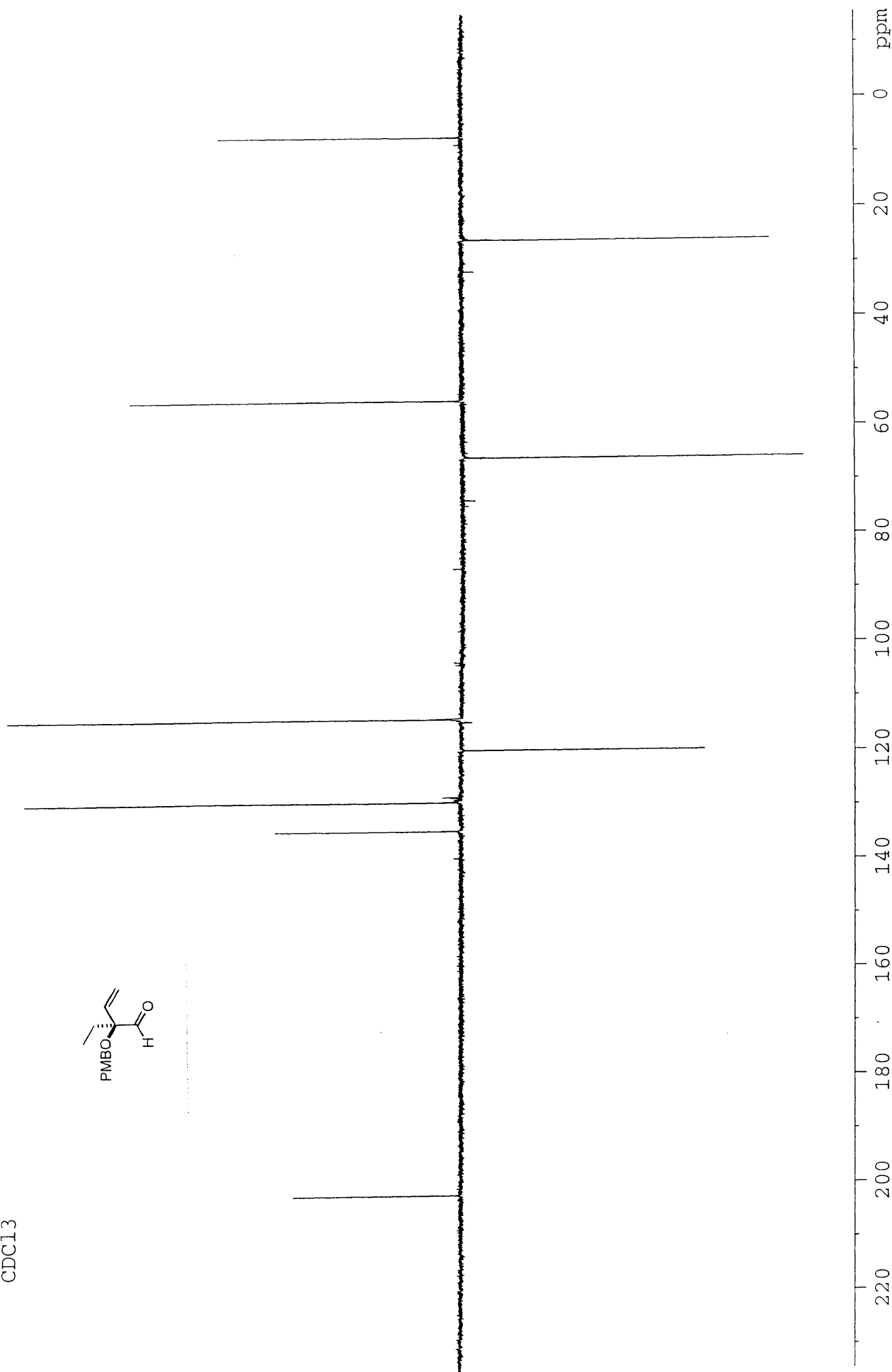
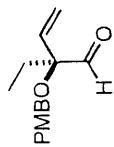
111-JG-18  
PROTON  
CDCl3



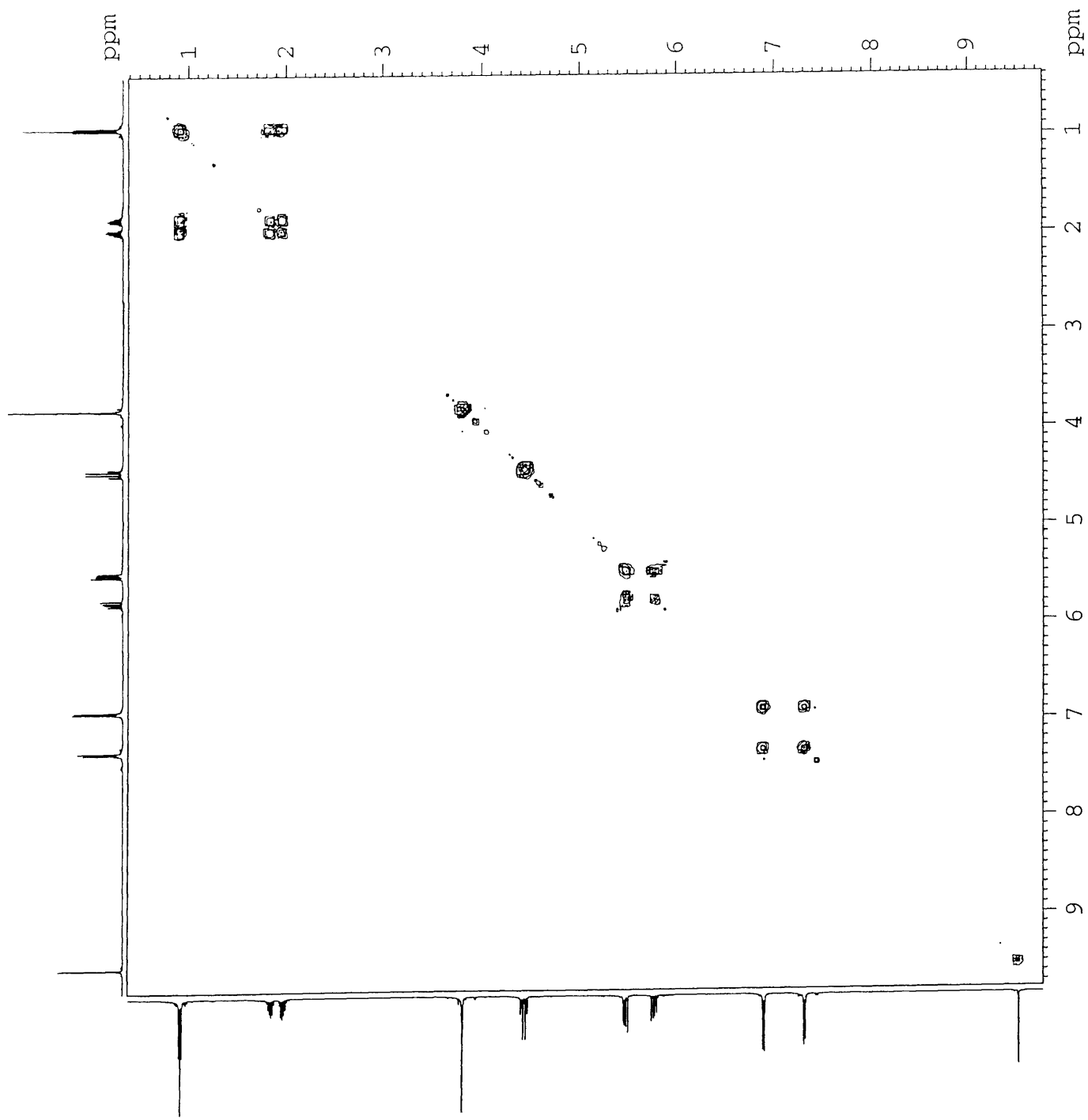
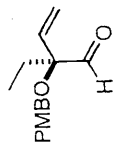
III-JG-18  
CARBON  
CDCl<sub>3</sub>



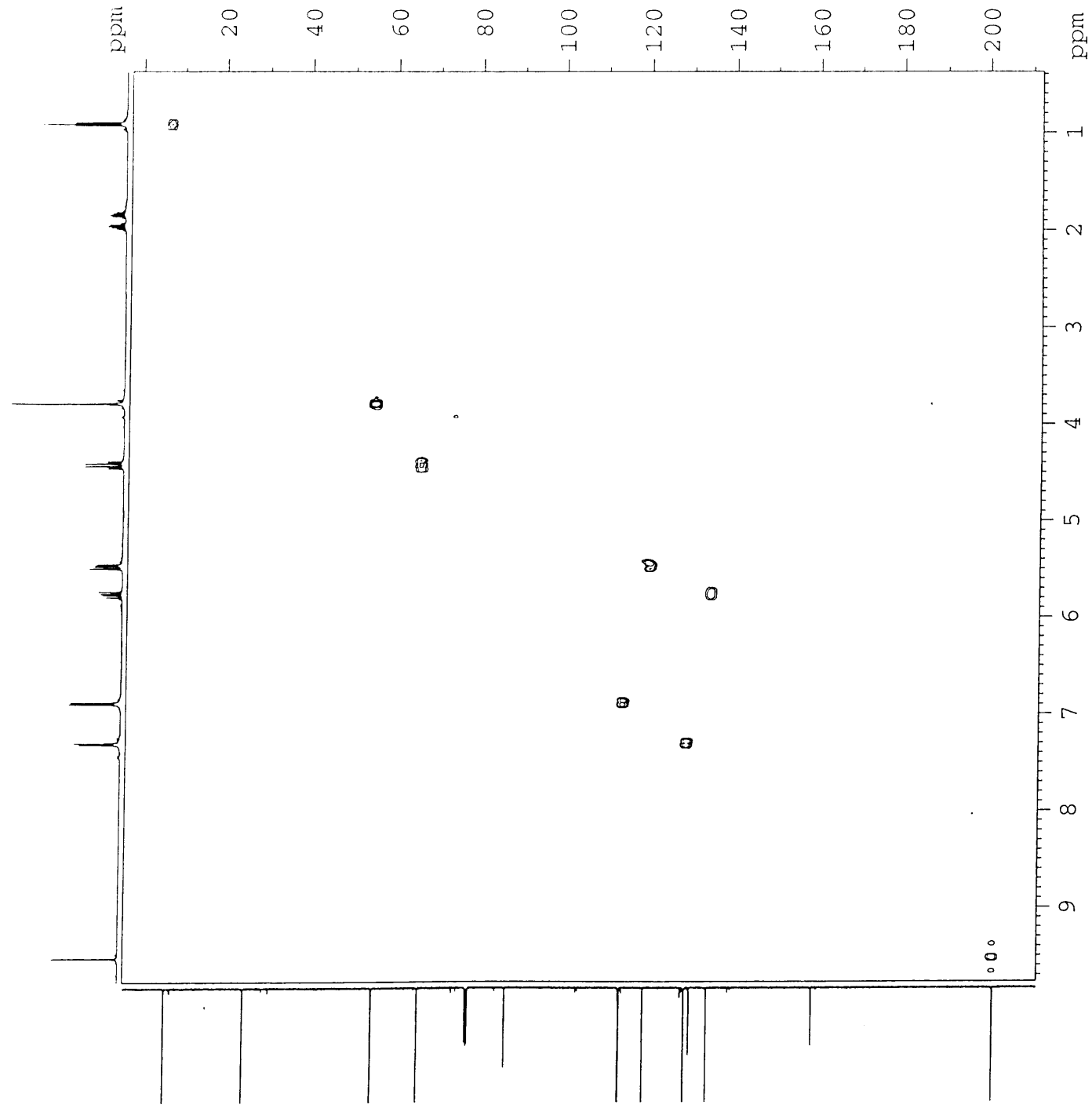
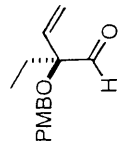
III-JG-18  
DEPT  
CDC13



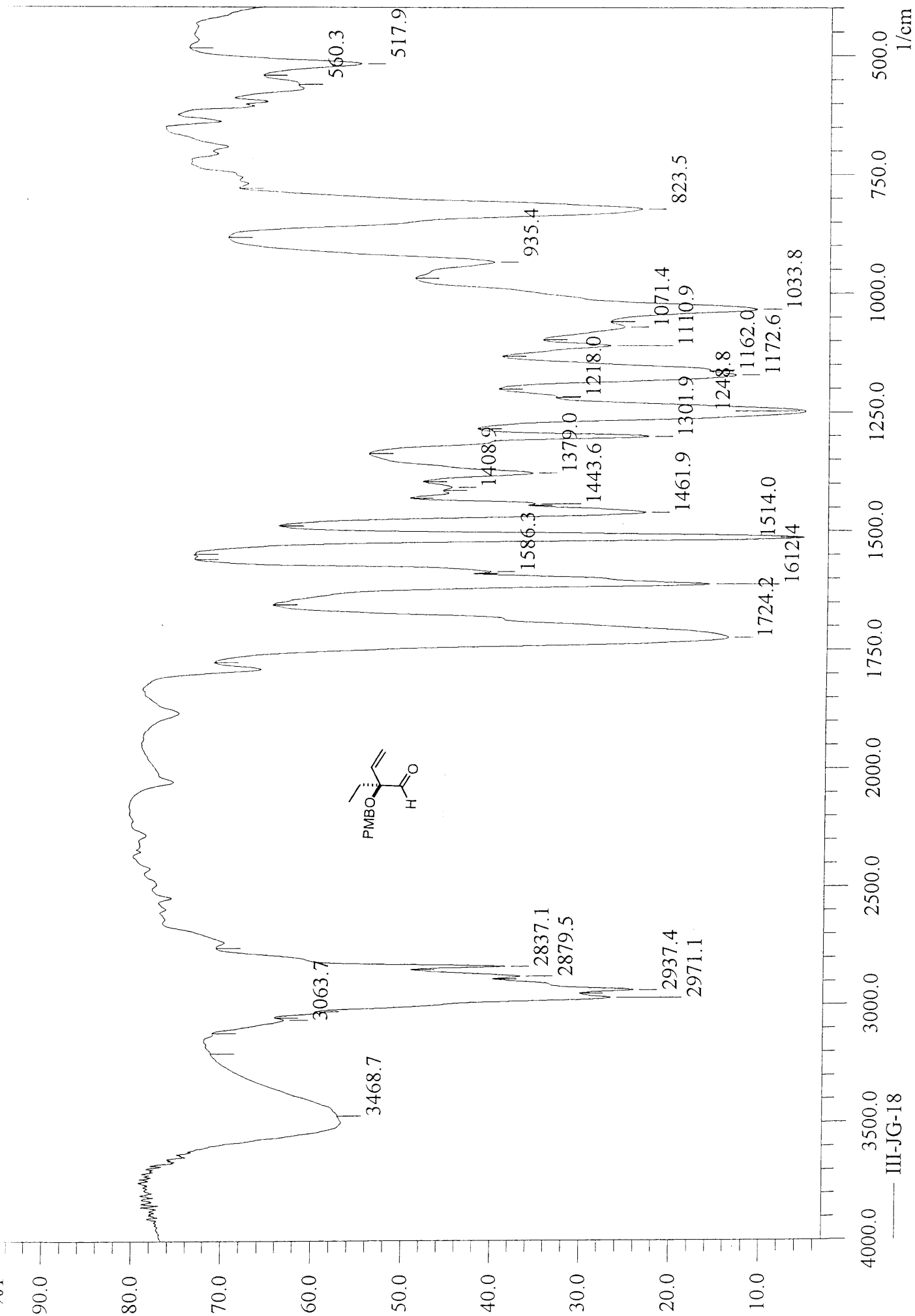
III-JG-18  
COSY  
CDCl<sub>3</sub>



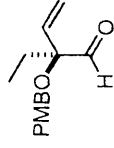
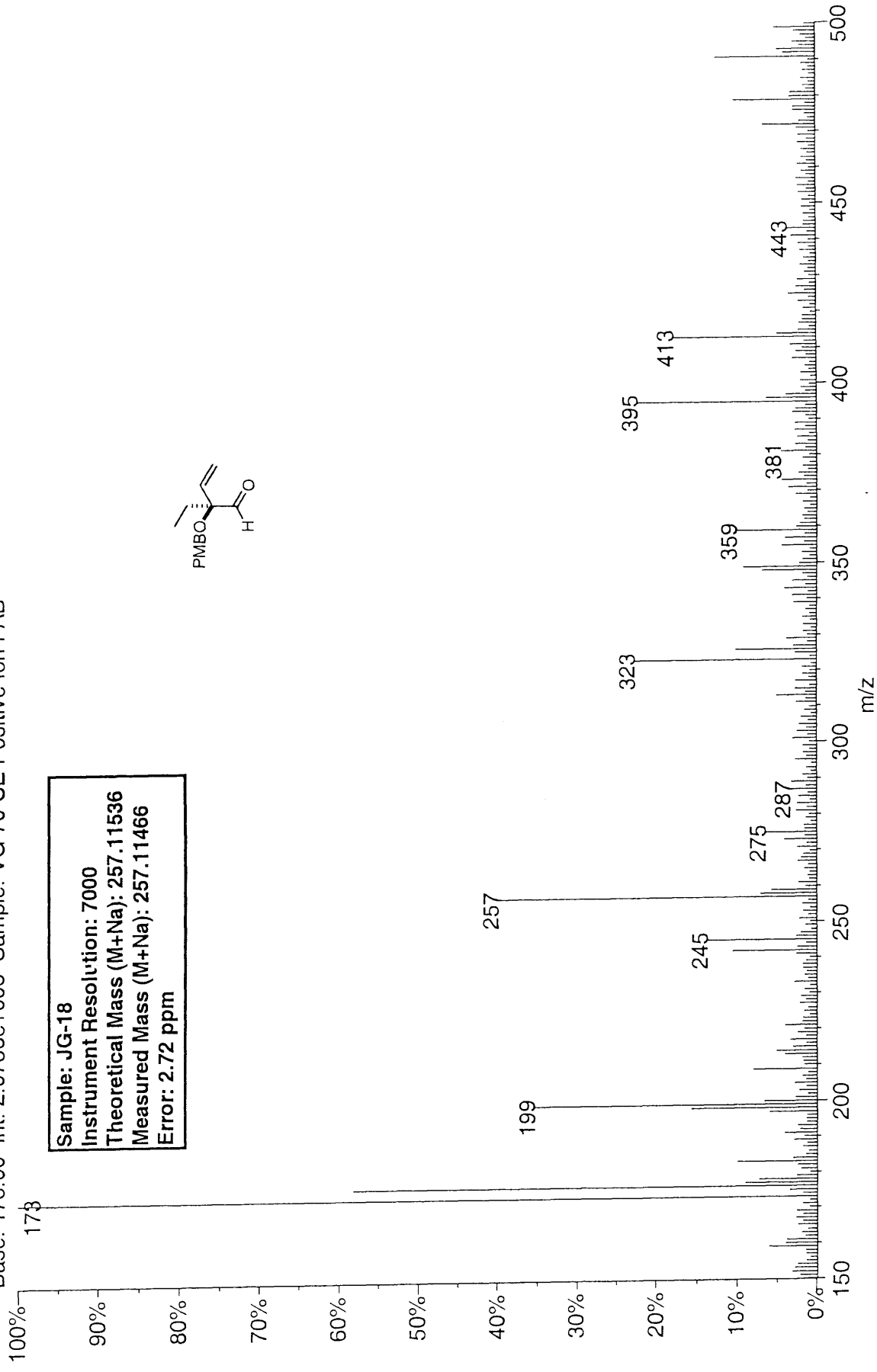
III-JG-18  
HMQC  
CDC13





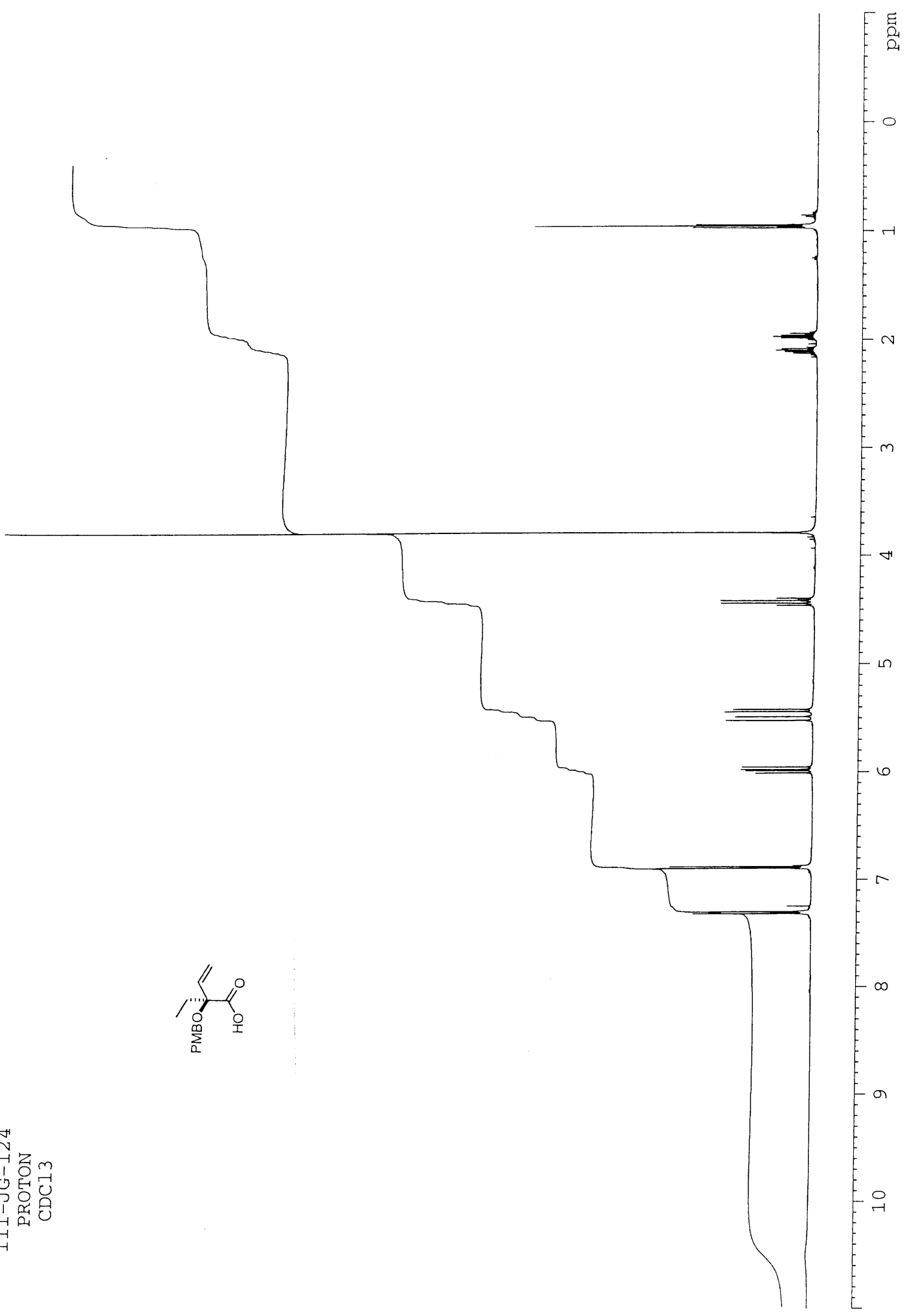
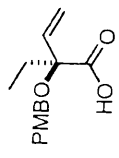


02170706: Scan 484 (96.70 min)  
Base: 173.00 Int: 2.0736e+006 Sample: VG 70-SE Positive Ion FAB

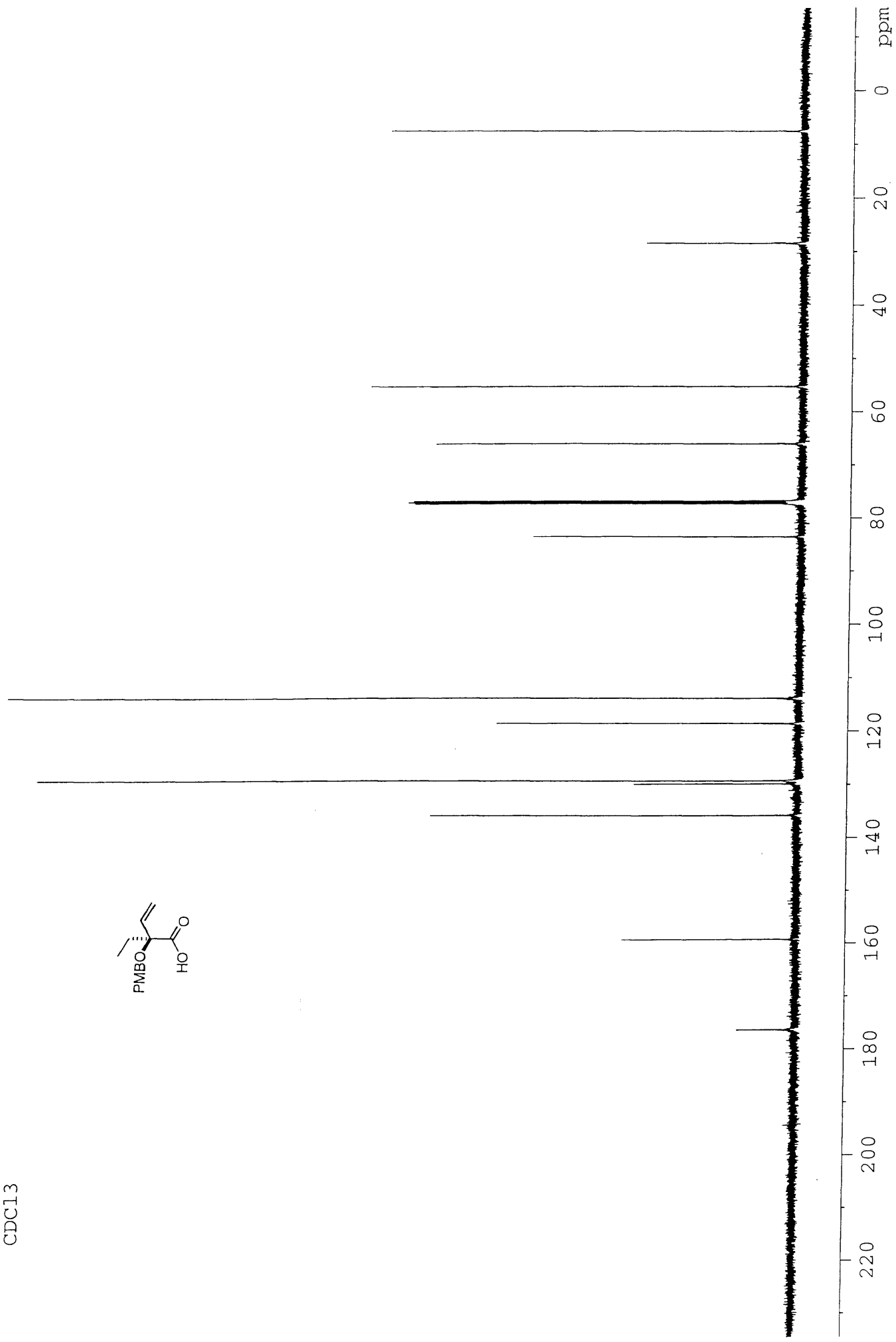
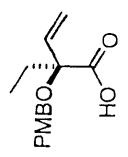


Sample: JG-18  
Instrument Resolution: 7000  
Theoretical Mass (M+Na): 257.11536  
Measured Mass (M+Na): 257.11466  
Error: 2.72 ppm

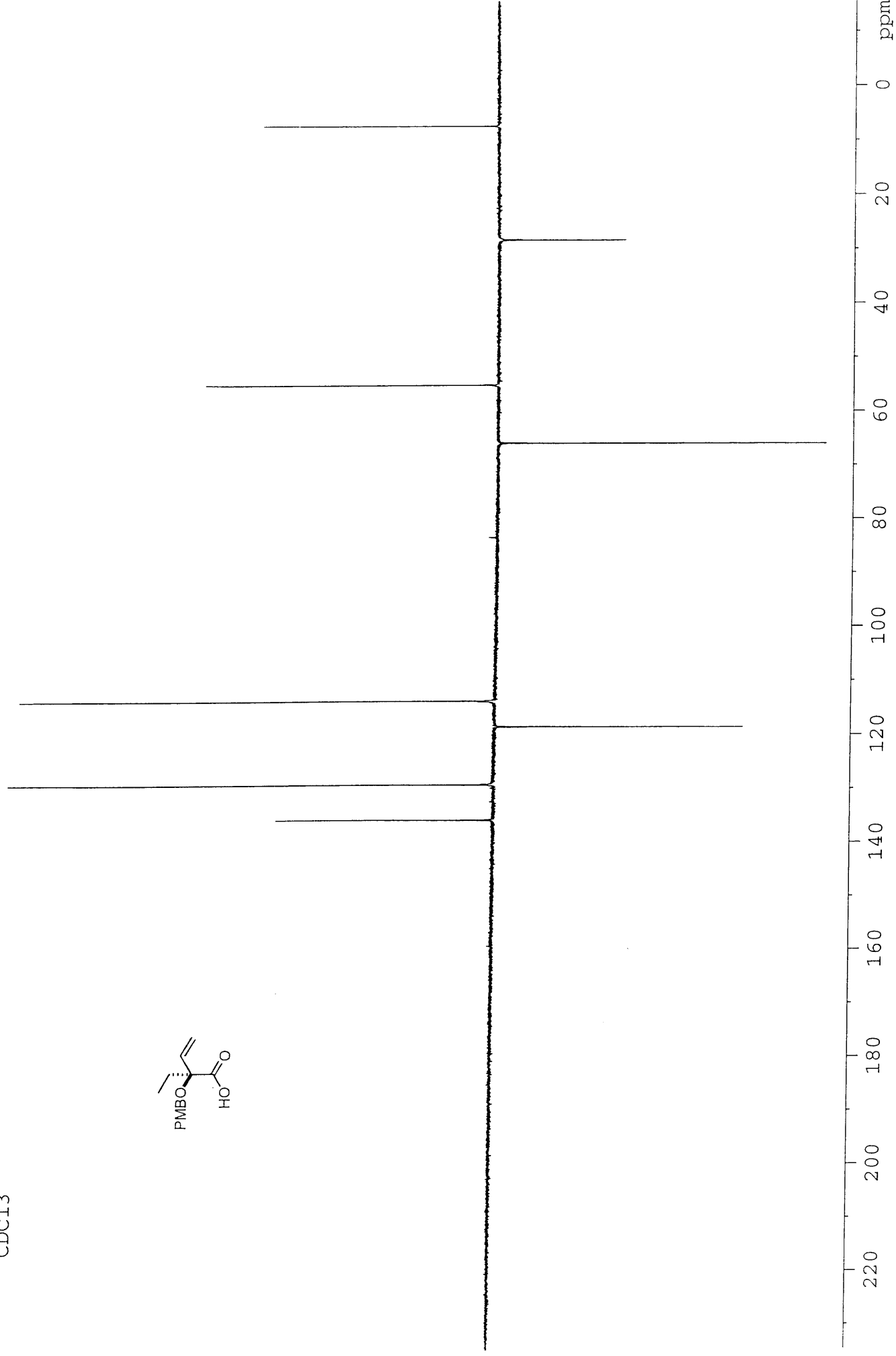
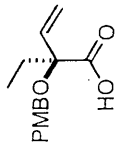
III-JG-124  
PROTON  
CDCl3



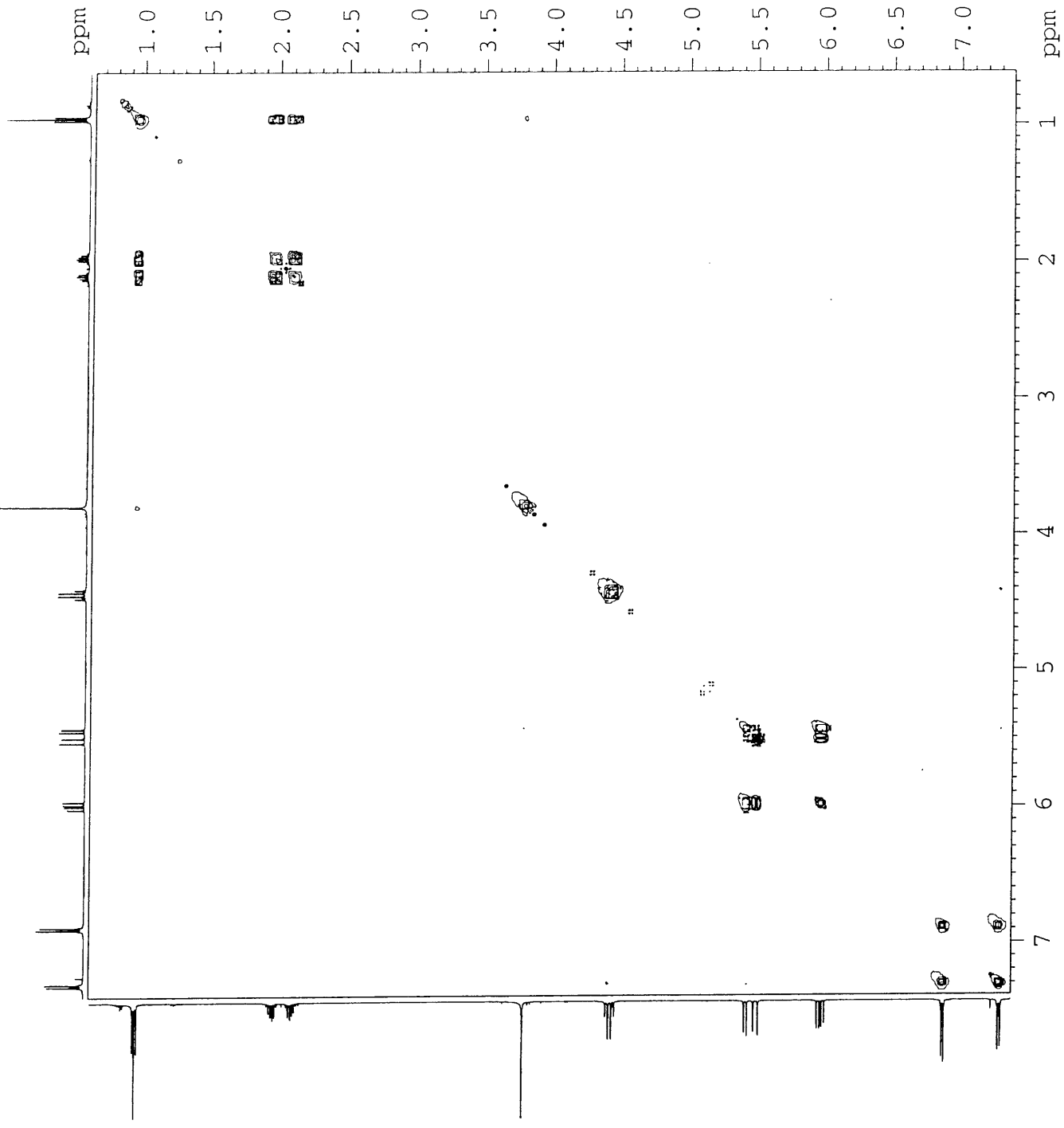
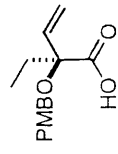
III-JG-124  
CARBON  
CDCl3



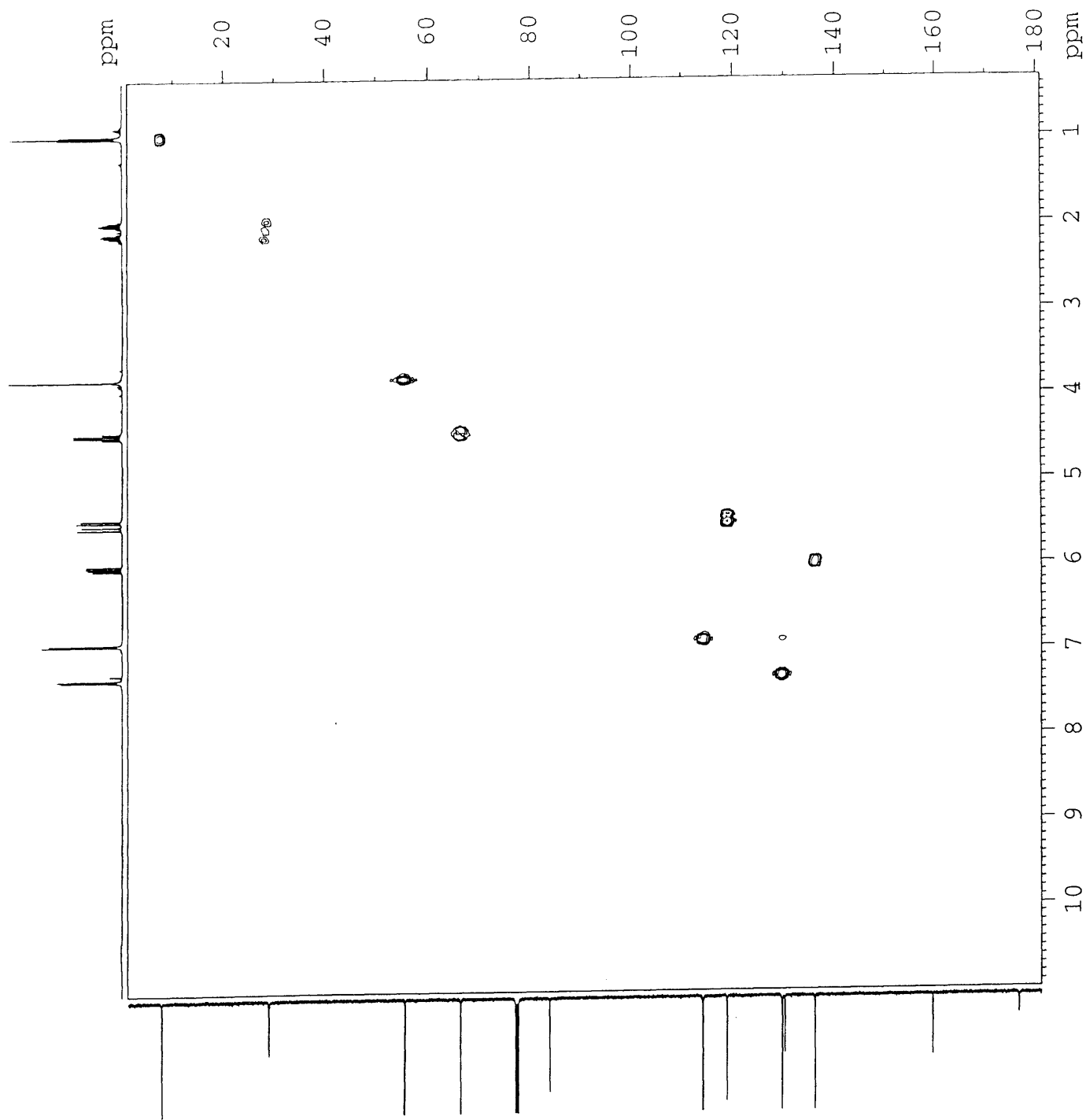
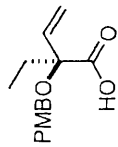
III-JG-124  
DEPT  
CDCl<sub>3</sub>

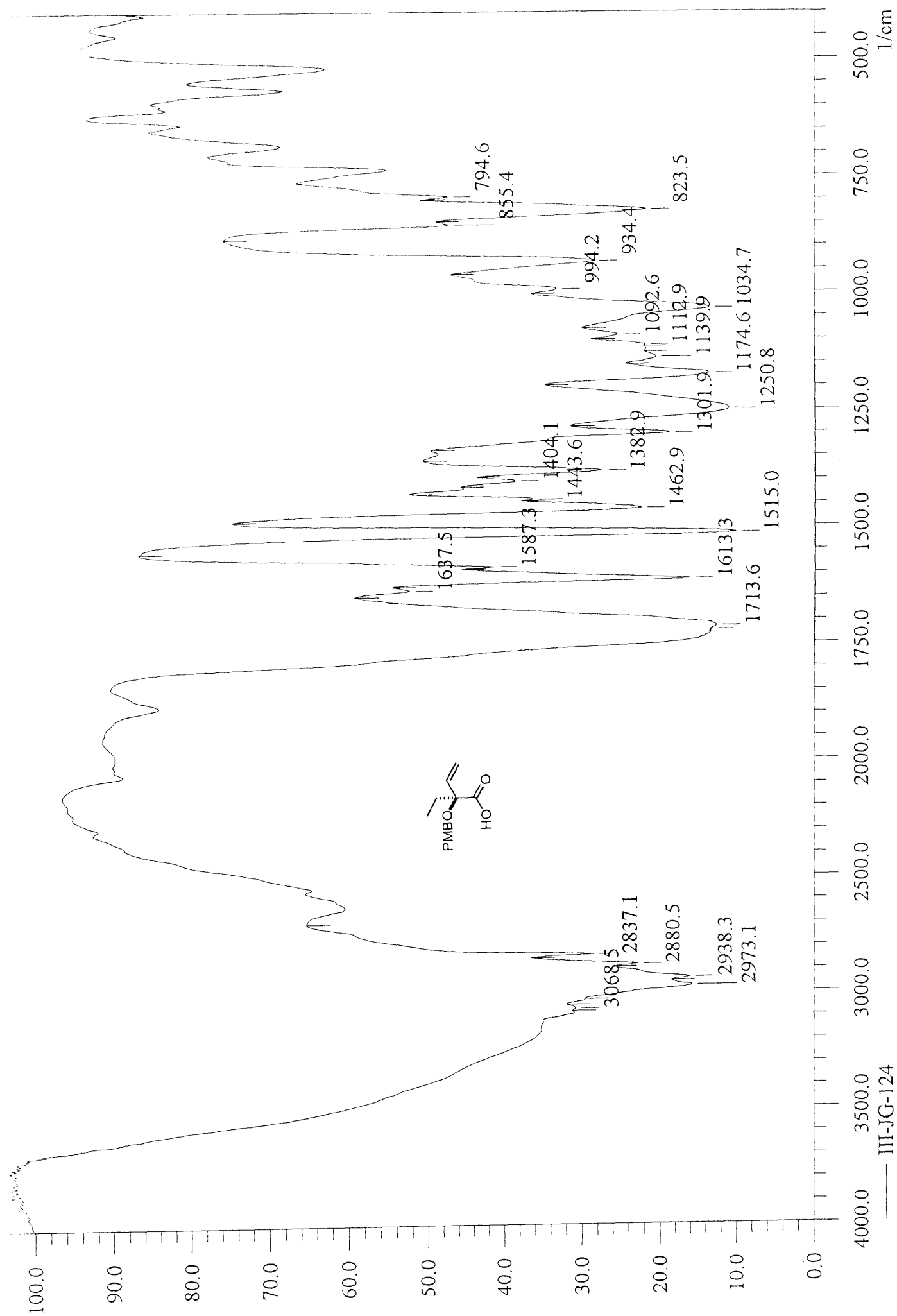


III-JG-124  
COSY  
CDCl<sub>3</sub>



III-JG-124  
HMOC  
CDC13

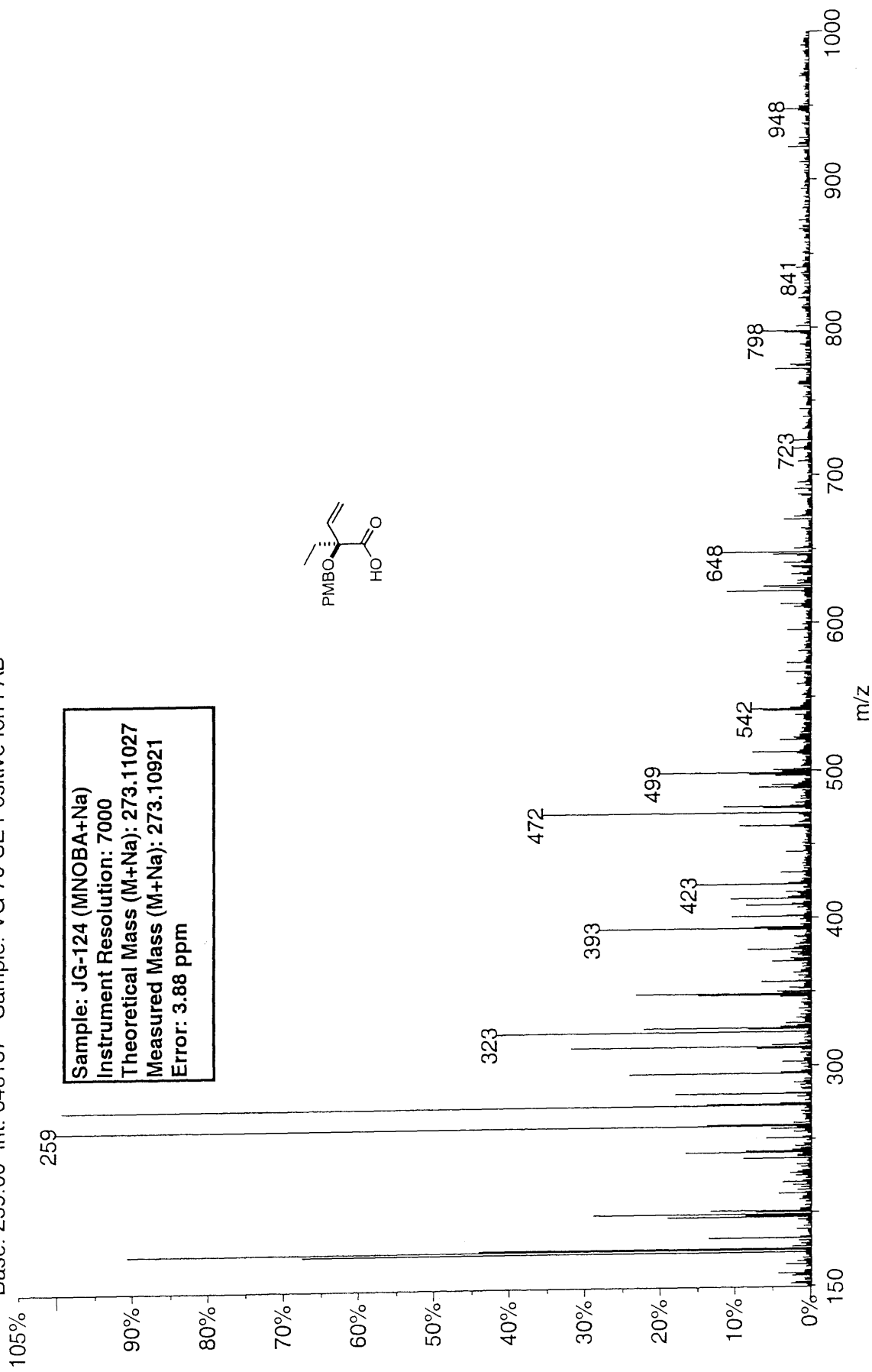




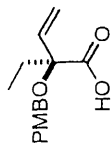
III-JG-124



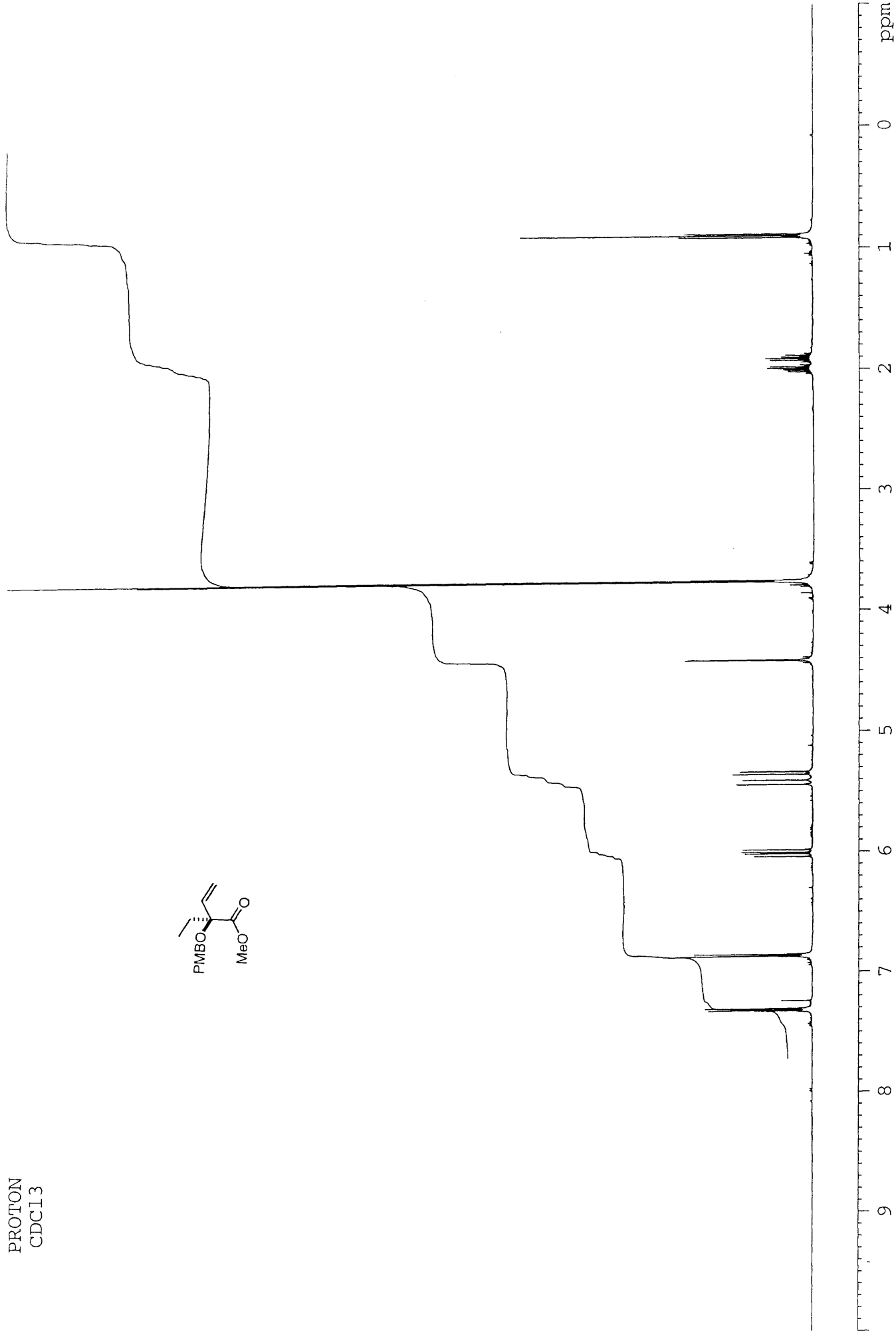
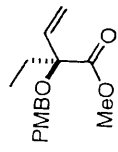
02170706: Scan 210 (41.90 min) - Back  
Base: 259.00 Int: 643187 Sample: VG 70-SE Positive Ion FAB



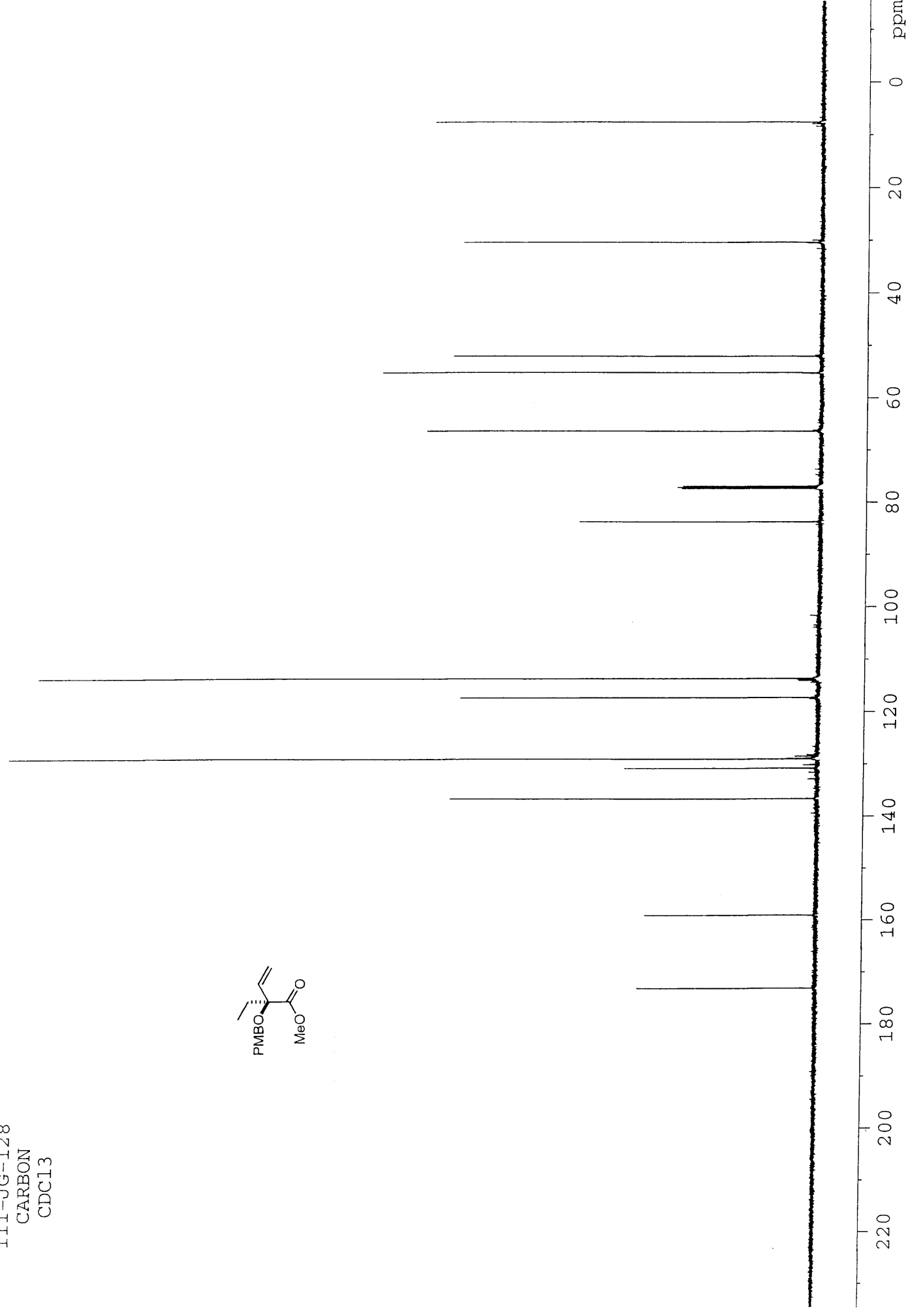
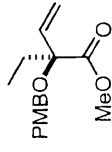
Sample: JG-124 (MNOBA+Na)  
Instrument Resolution: 7000  
Theoretical Mass (M+Na): 273.11027  
Measured Mass (M+Na): 273.10921  
Error: 3.88 ppm



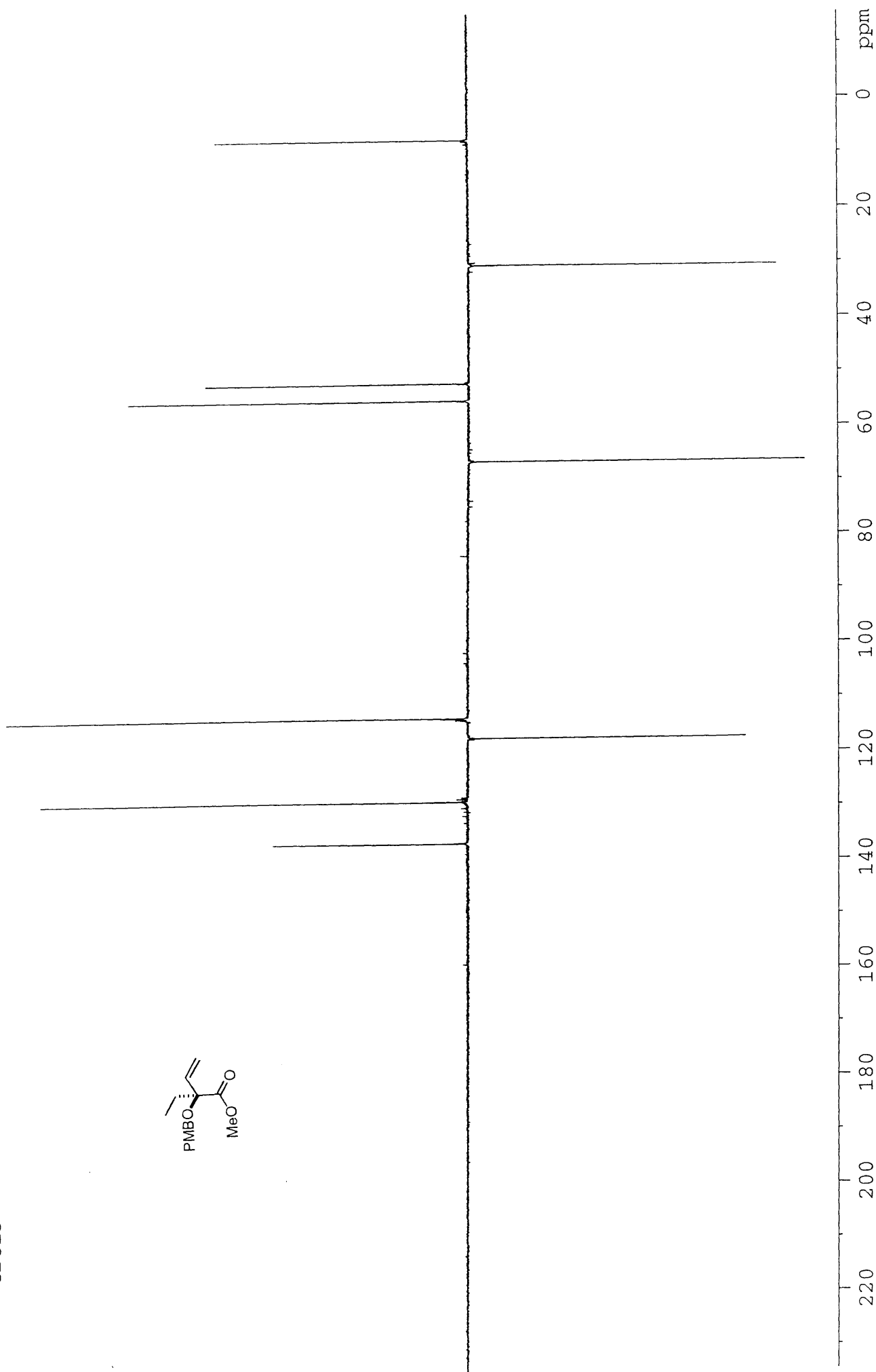
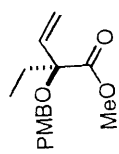
III-JG-128  
PROTON  
CDCl<sub>3</sub>



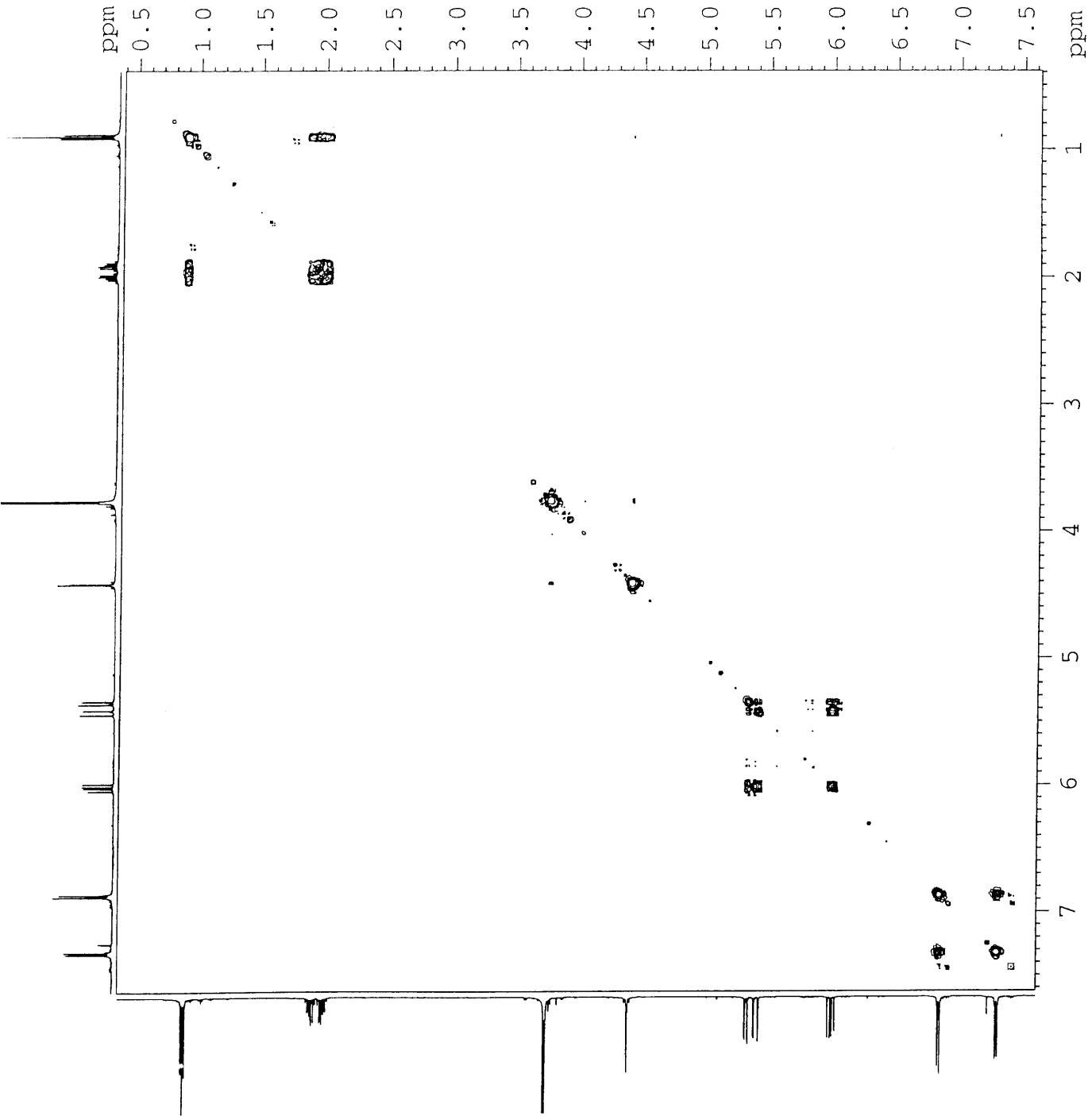
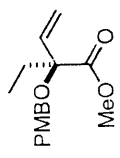
III-JG-128  
CARBON  
CDCl<sub>3</sub>



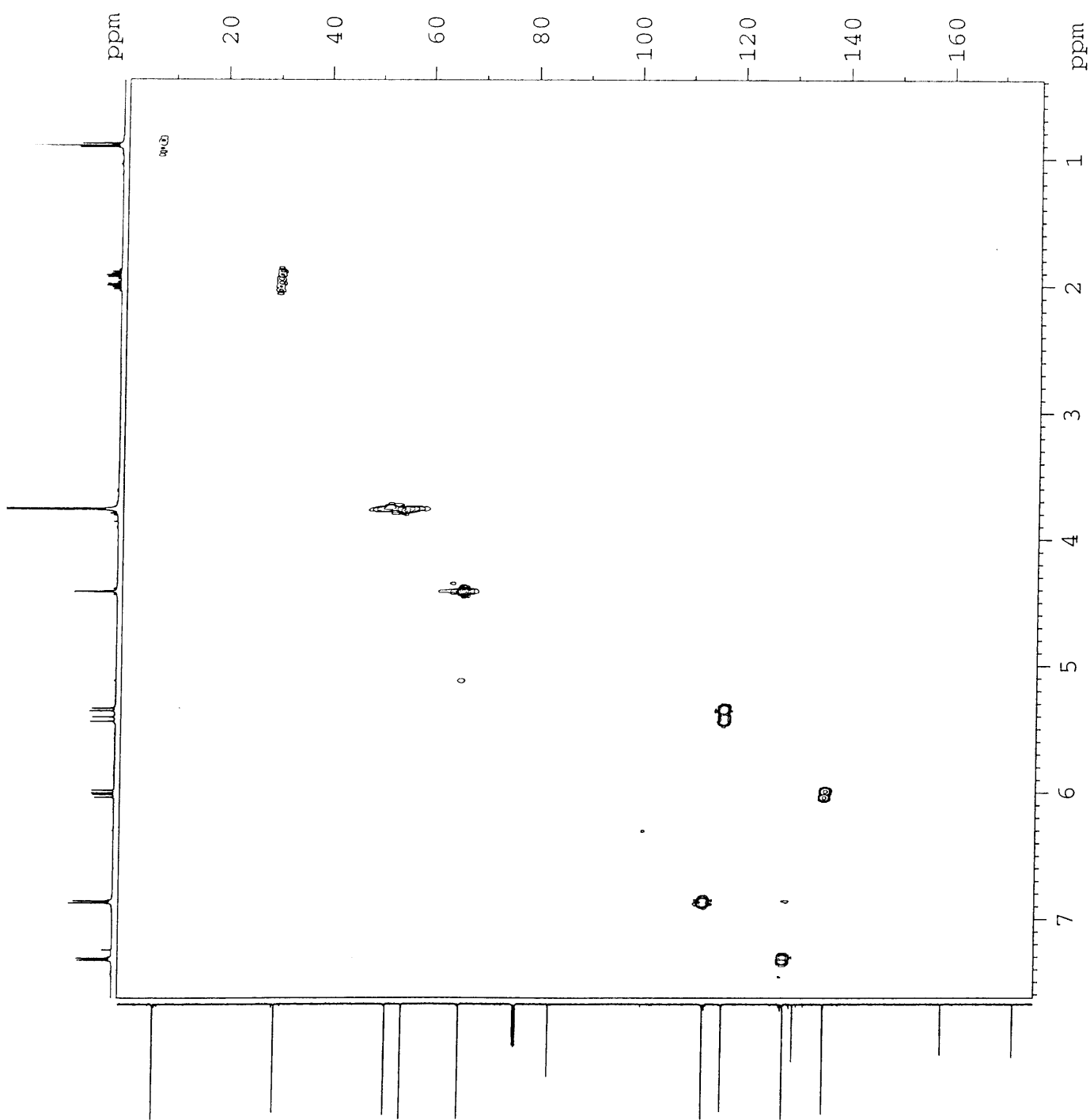
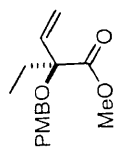
III-JG-128  
DEPT  
CDCl<sub>3</sub>

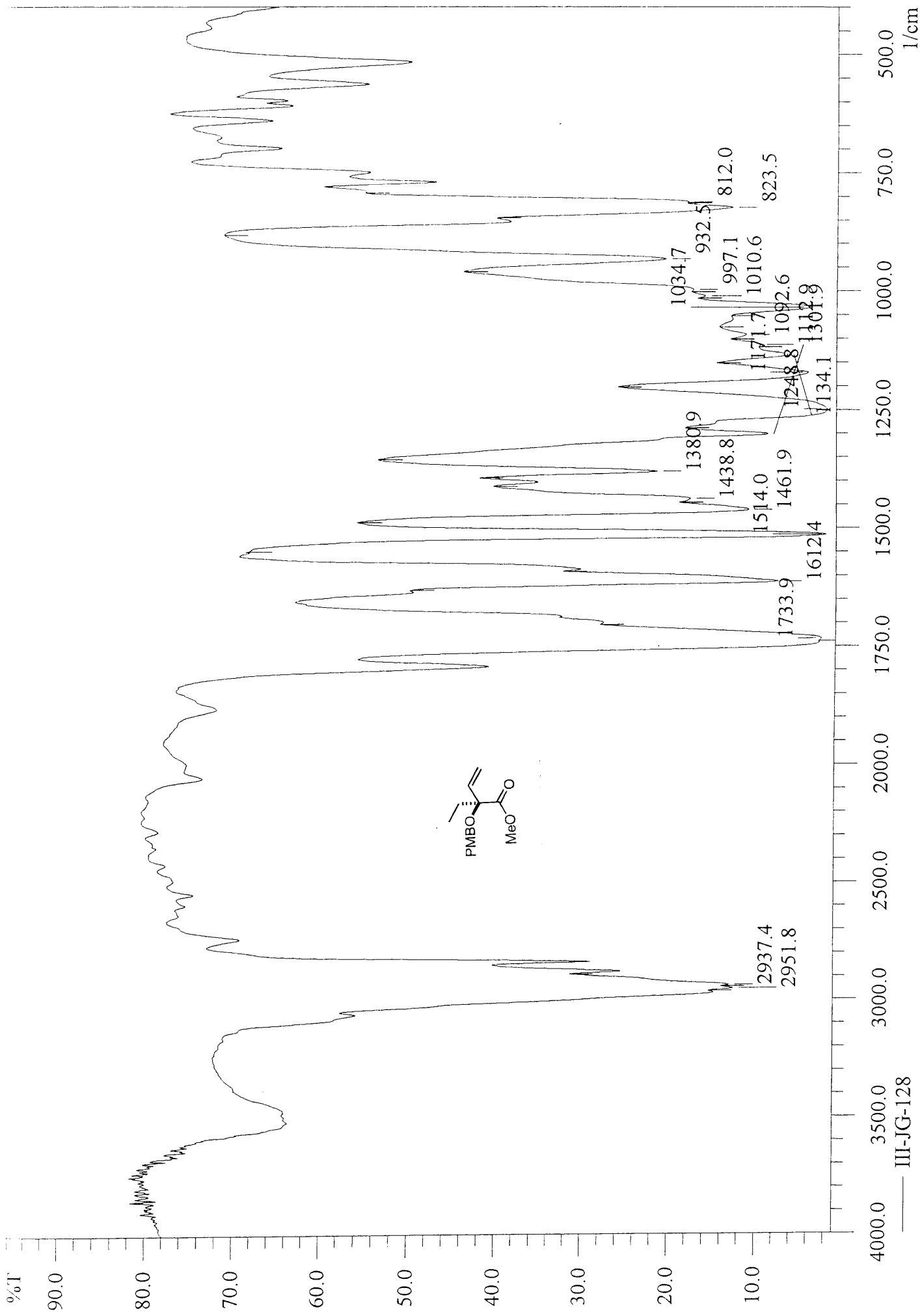


III-JG-128  
COSY  
CDCl3

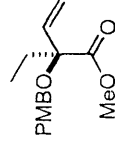
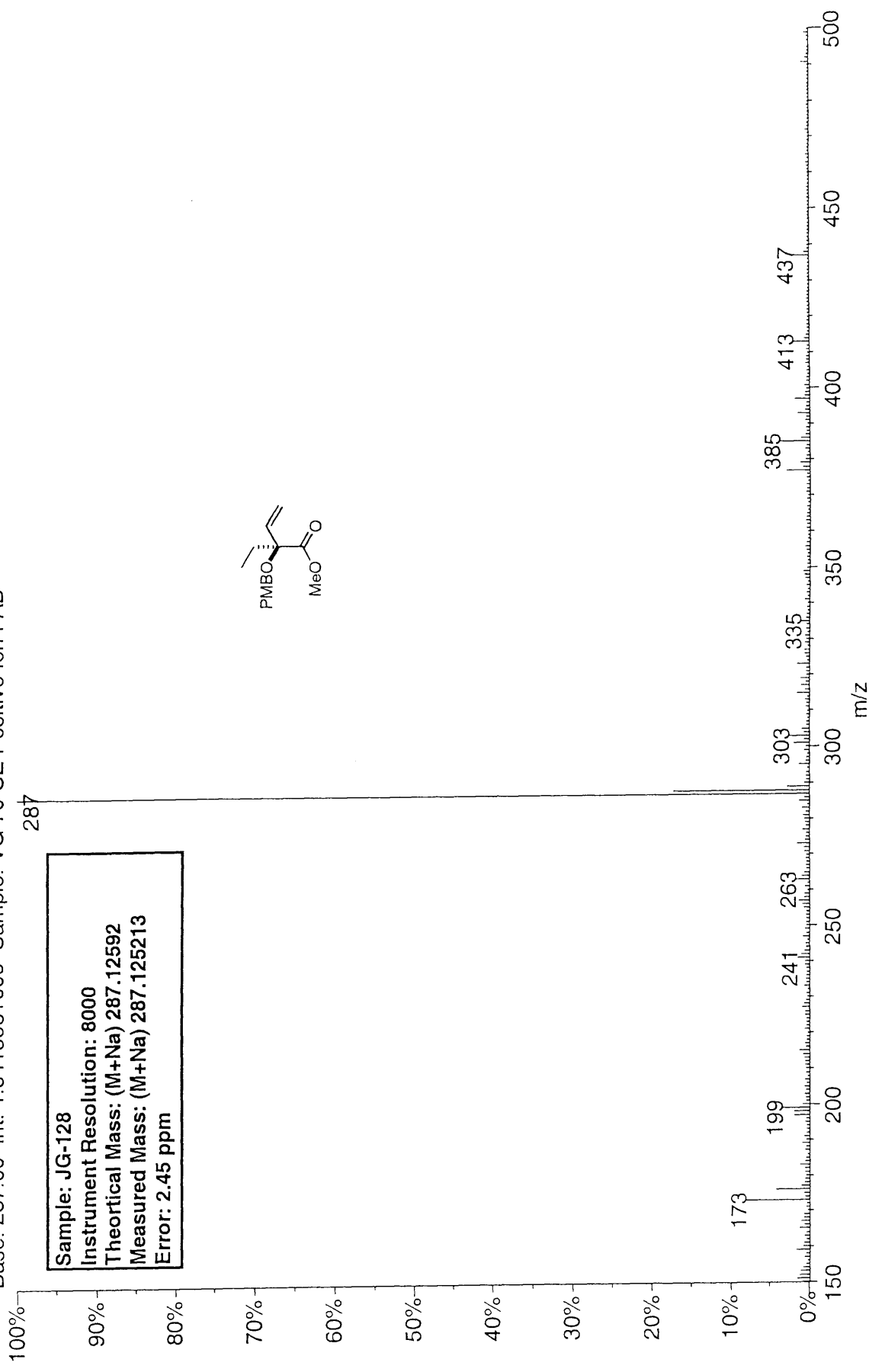


III-JG-128  
HMQC  
CDC13



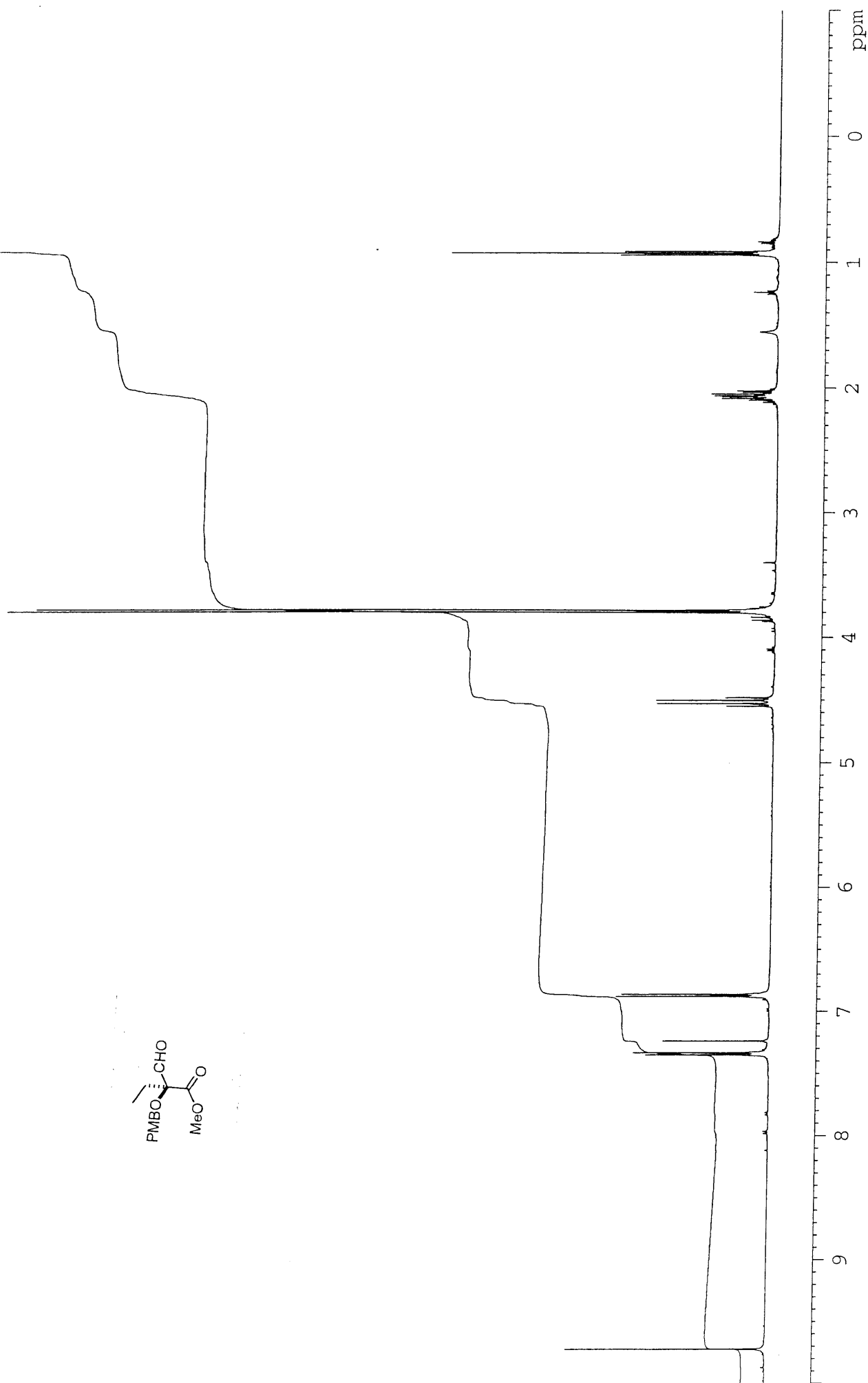
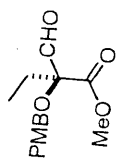


02170706: Scan Avg 289-294 (57.70 - 58.70 min)  
Base: 287.00 Int: 1.54133e+006 Sample: VG 70-SE Positive Ion FAB

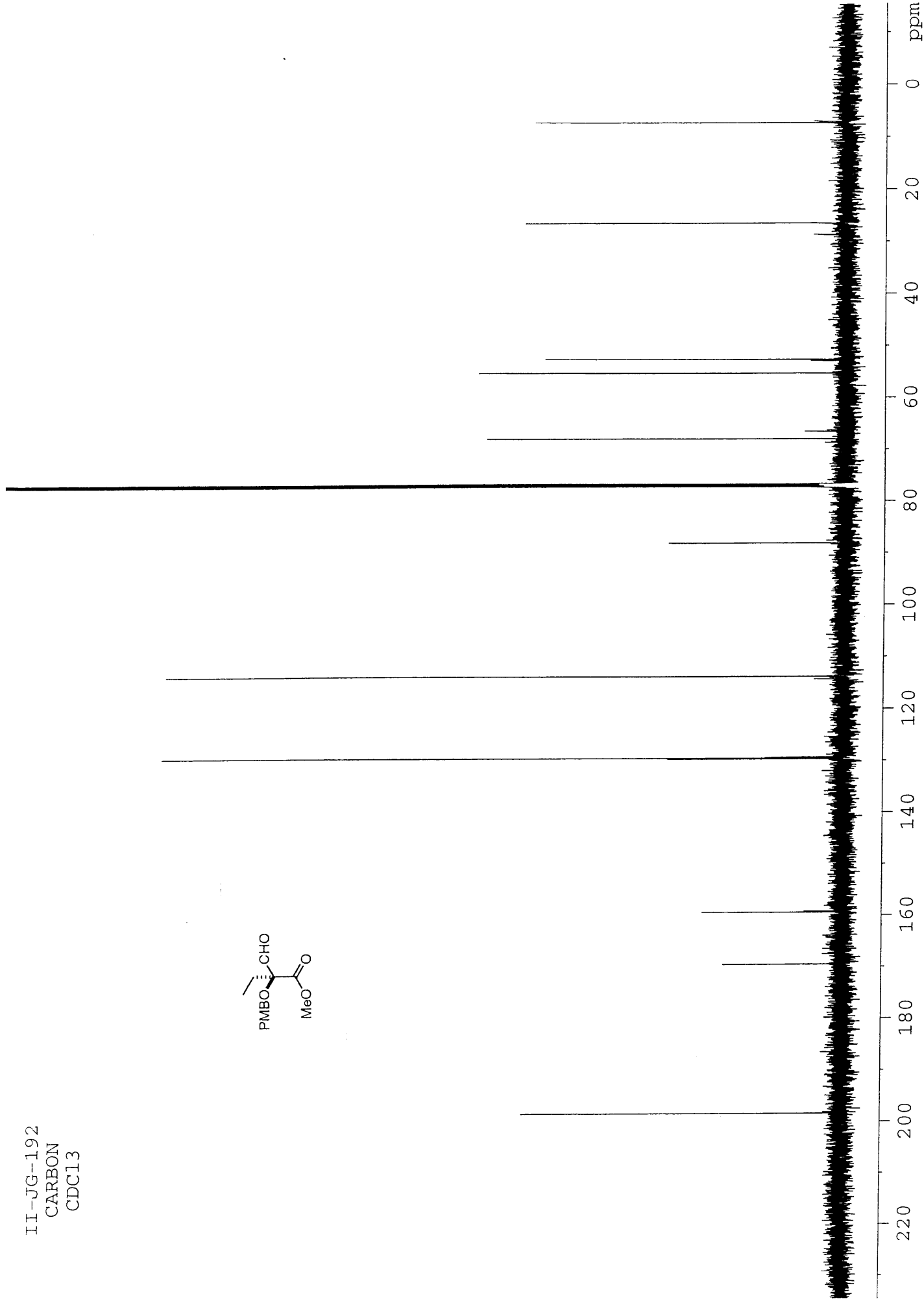
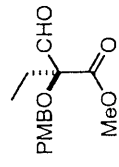




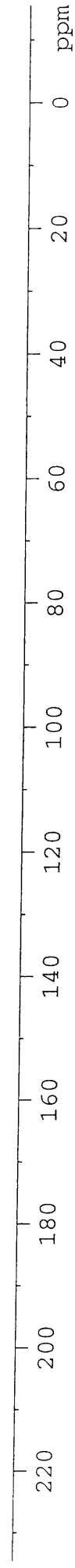
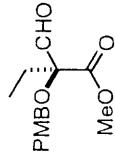
II-JG-192  
PROTON  
CDCl<sub>3</sub>



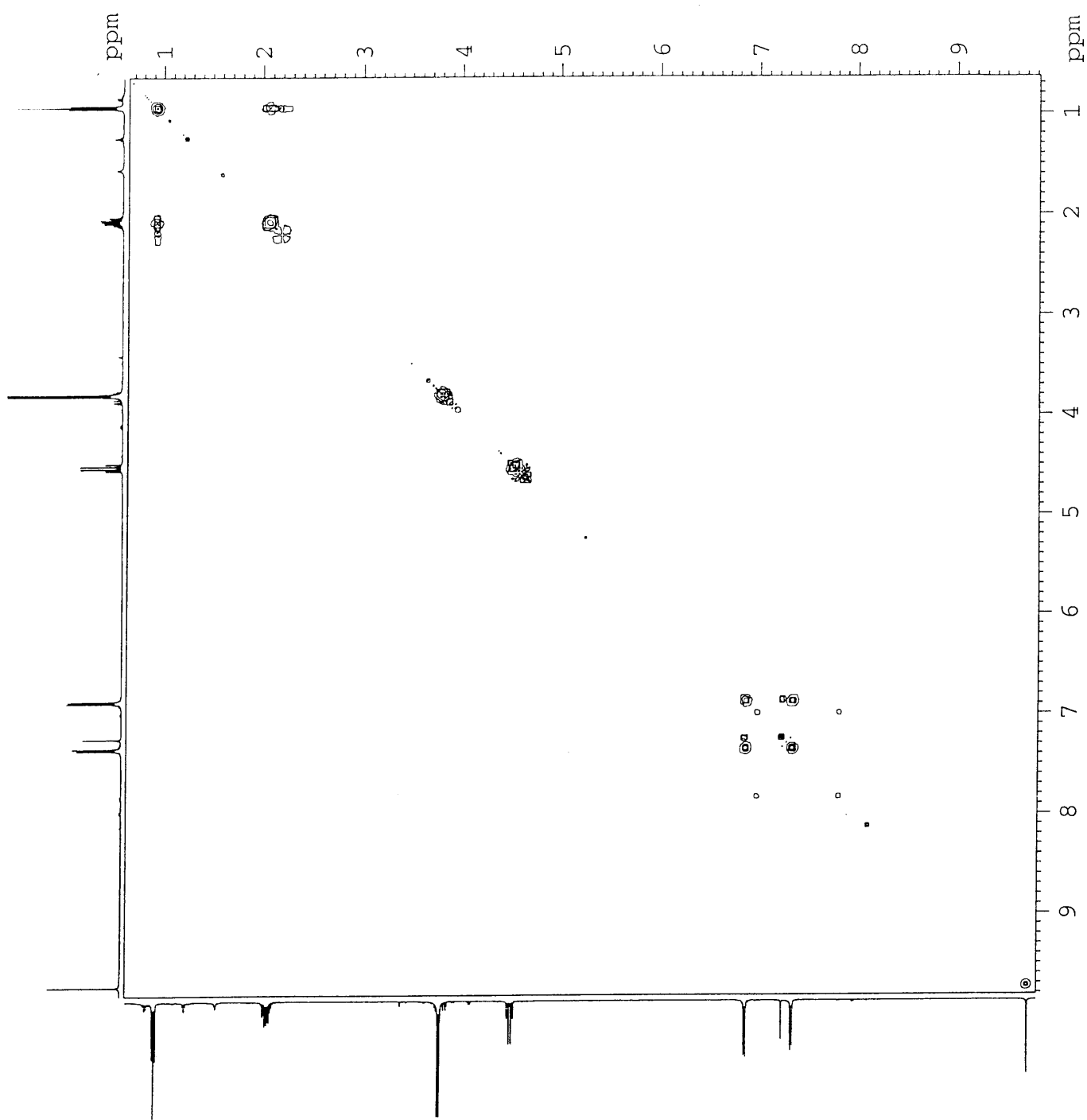
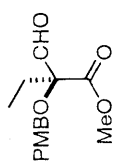
II-JG--192  
CARBON  
CDCl<sub>3</sub>



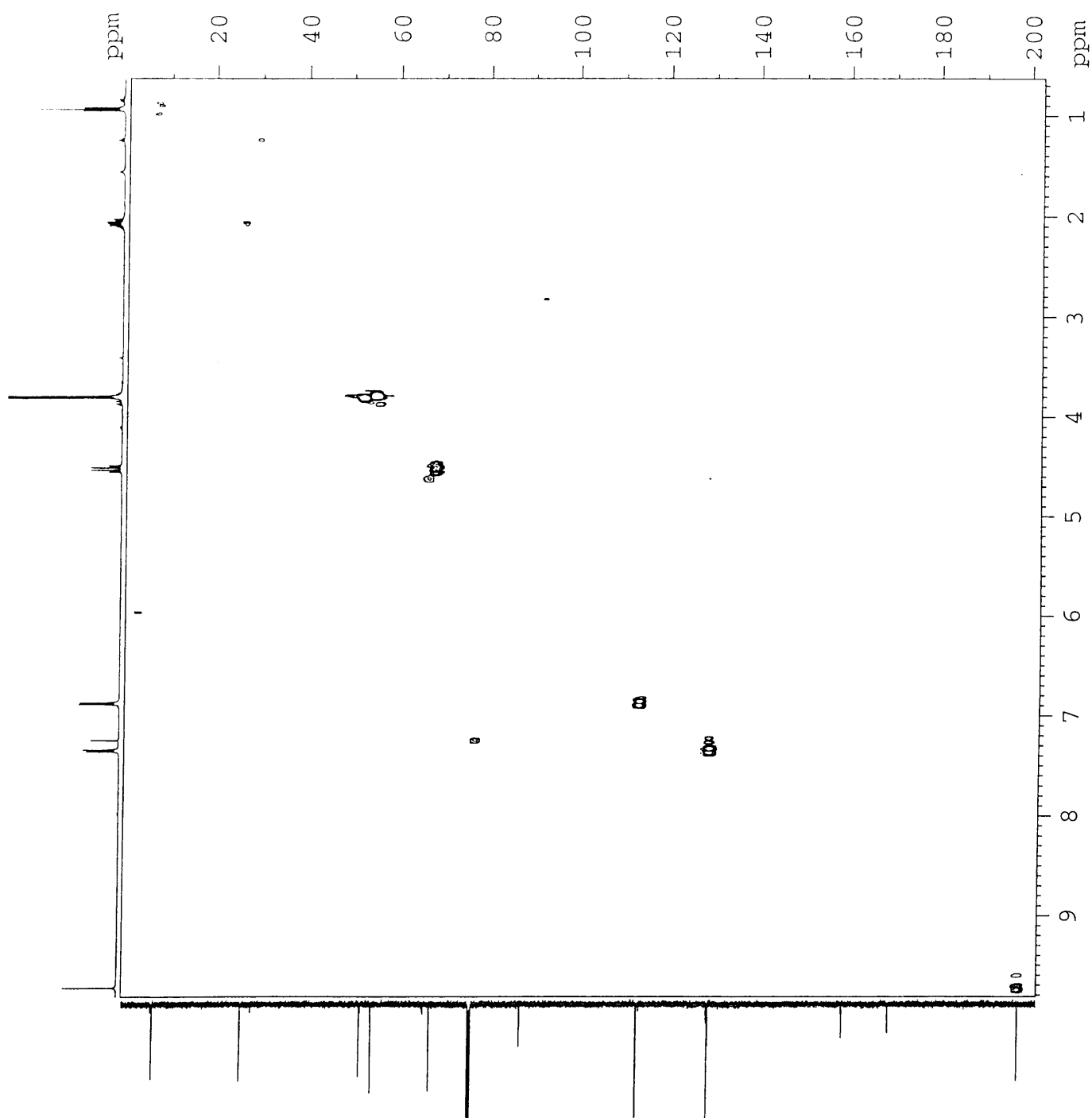
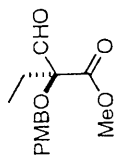
II-JG-192  
DEPT  
CDCl<sub>3</sub>

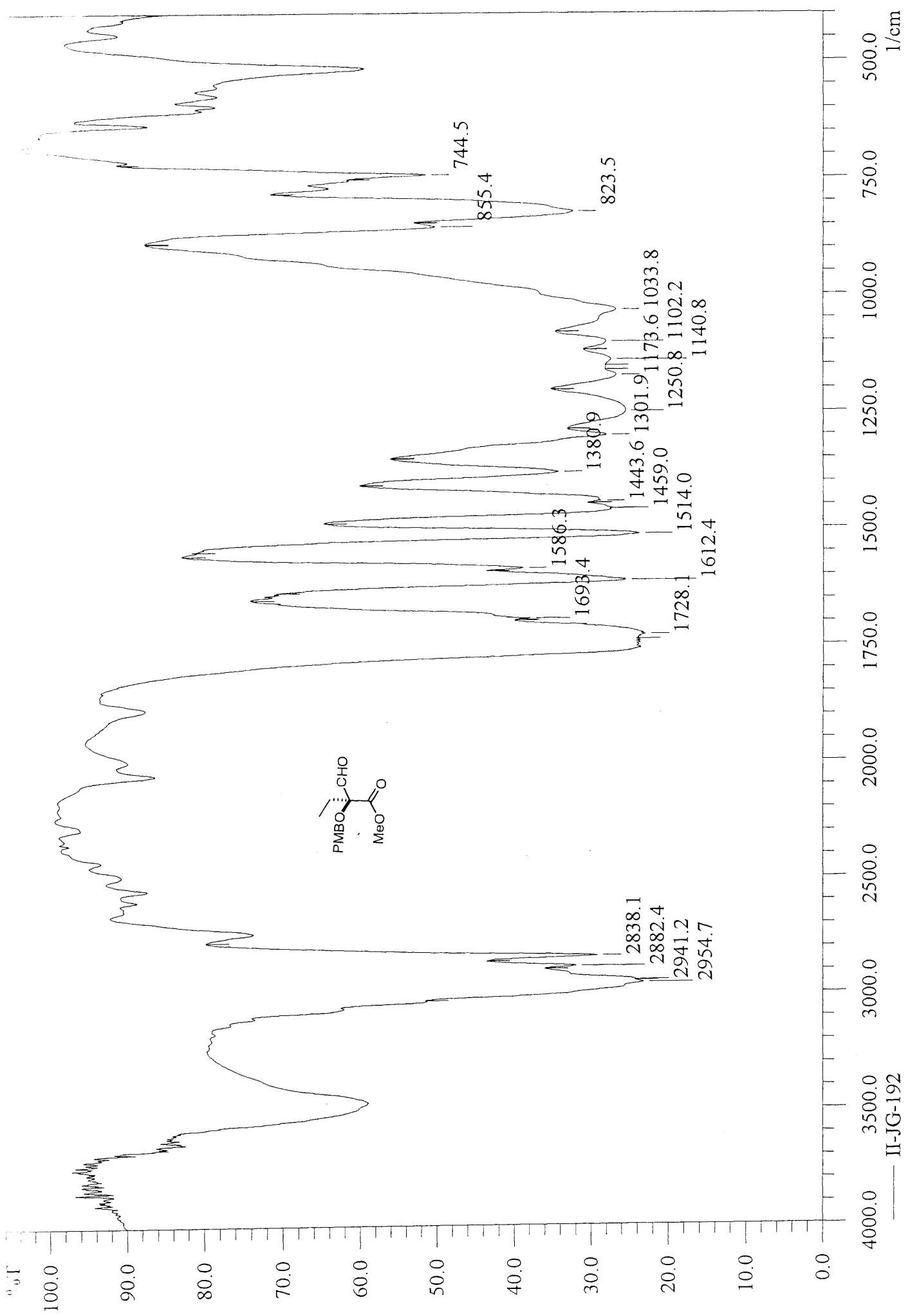


II-JG-192  
COSY  
CDCl<sub>3</sub>



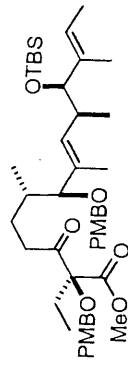
II-JG-192  
HMQC  
CDCl<sub>3</sub>



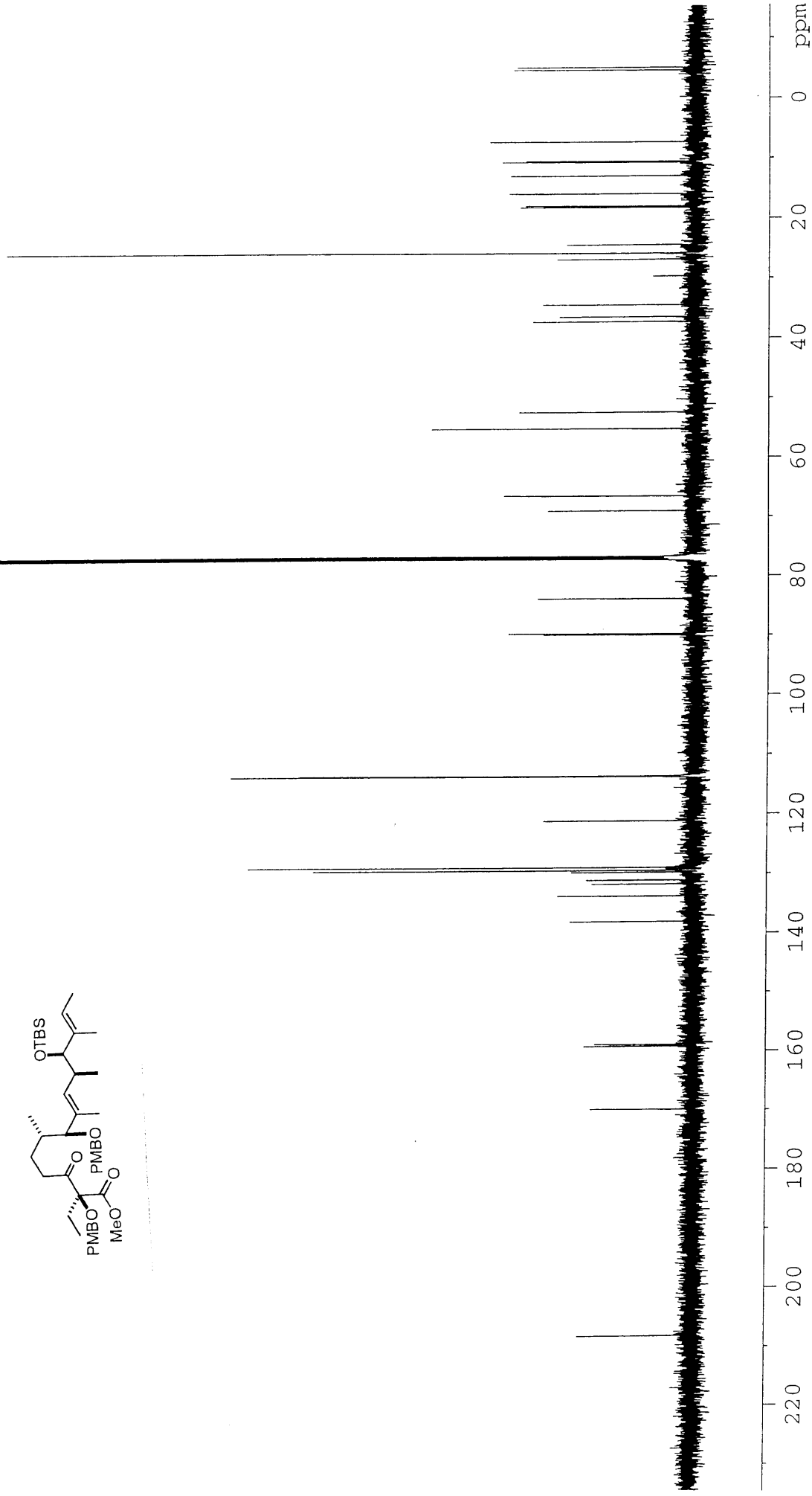
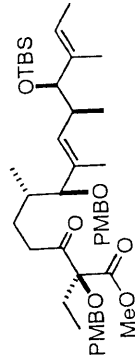


II-JG-192

III-JG-188  
PROTON  
CDCl<sub>3</sub>

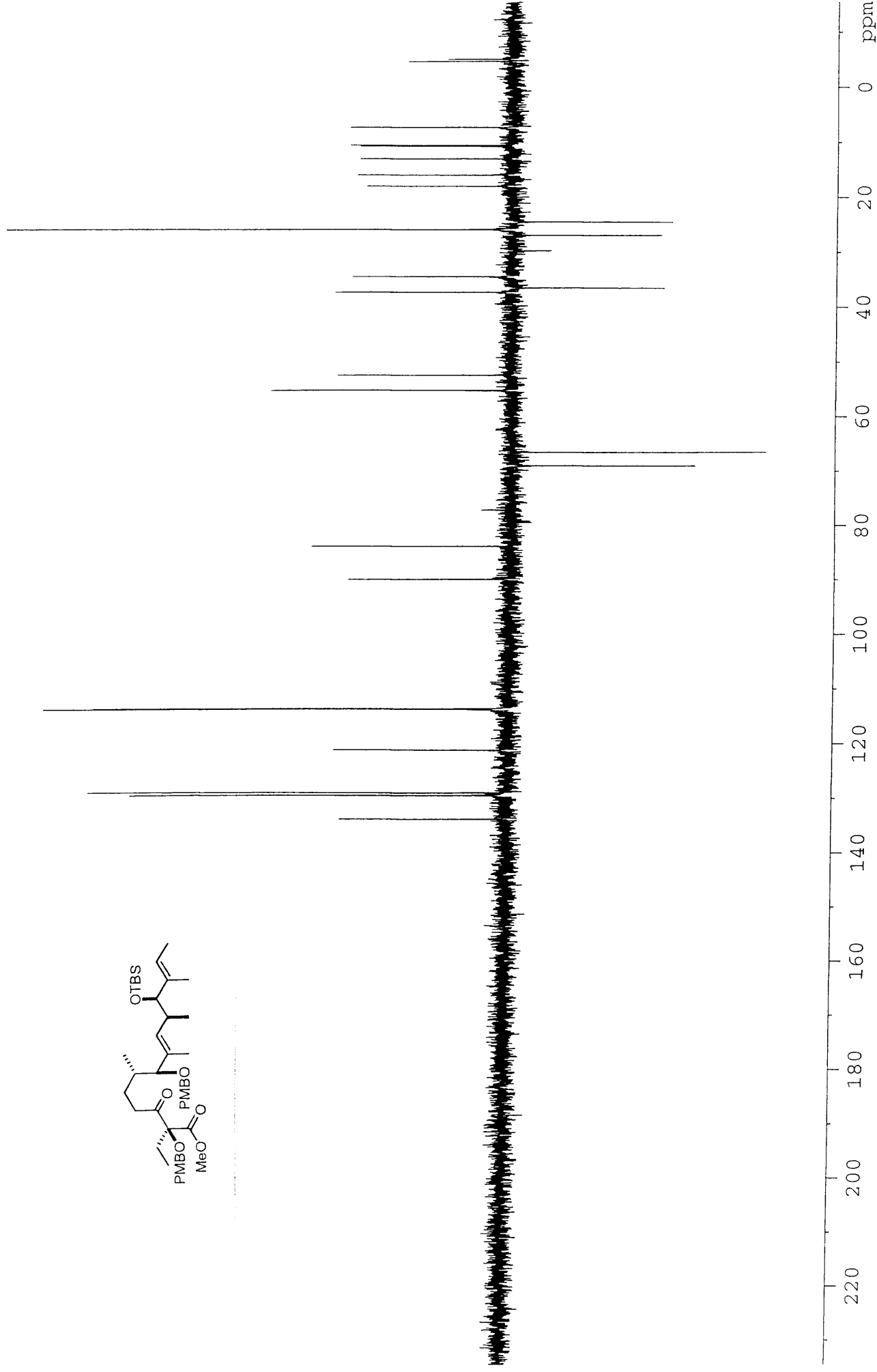
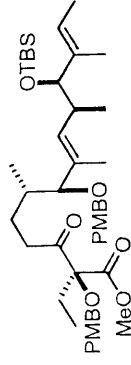


III-JG--188  
CARBON  
CDC13

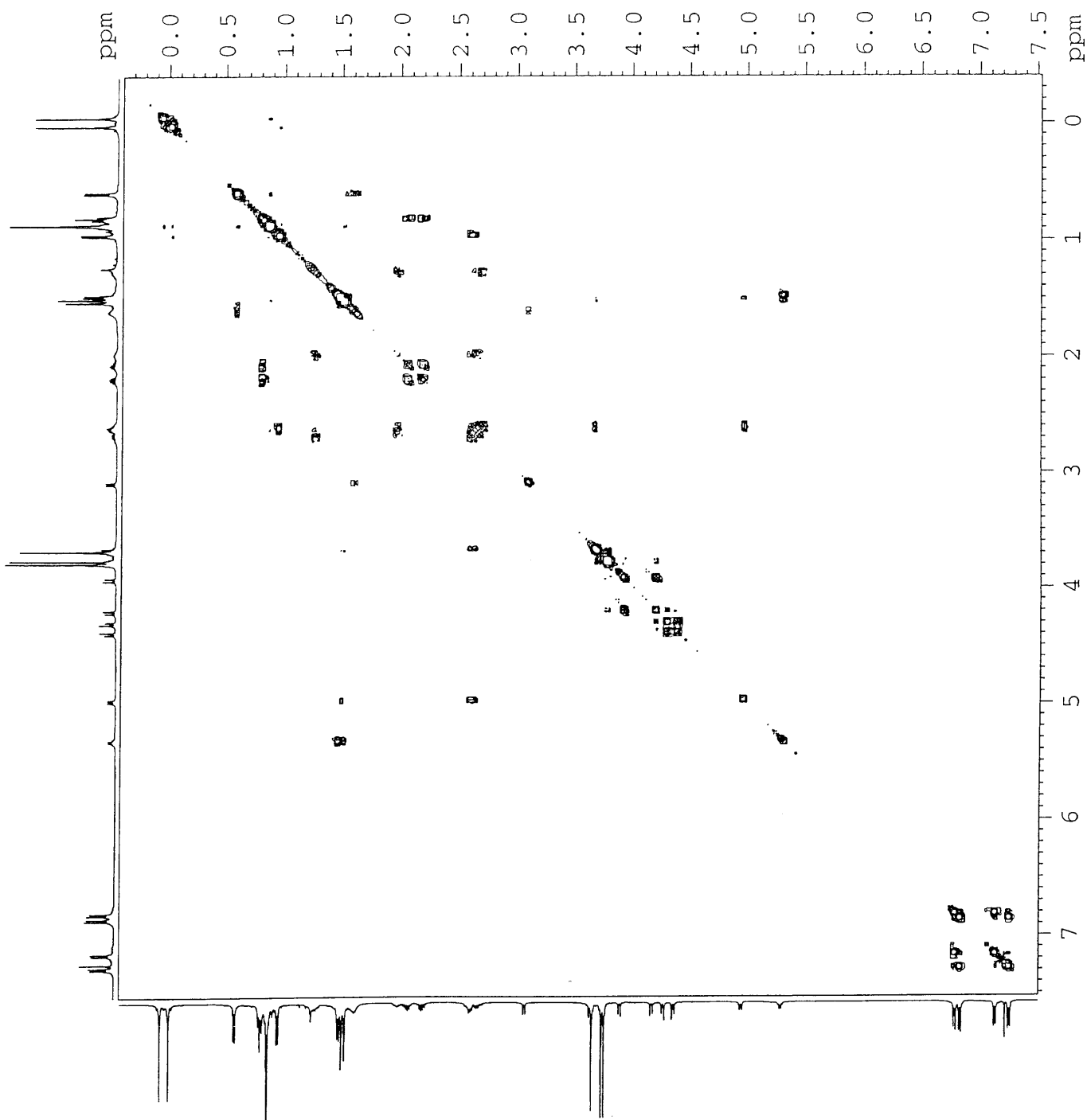
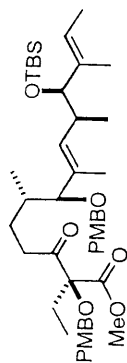




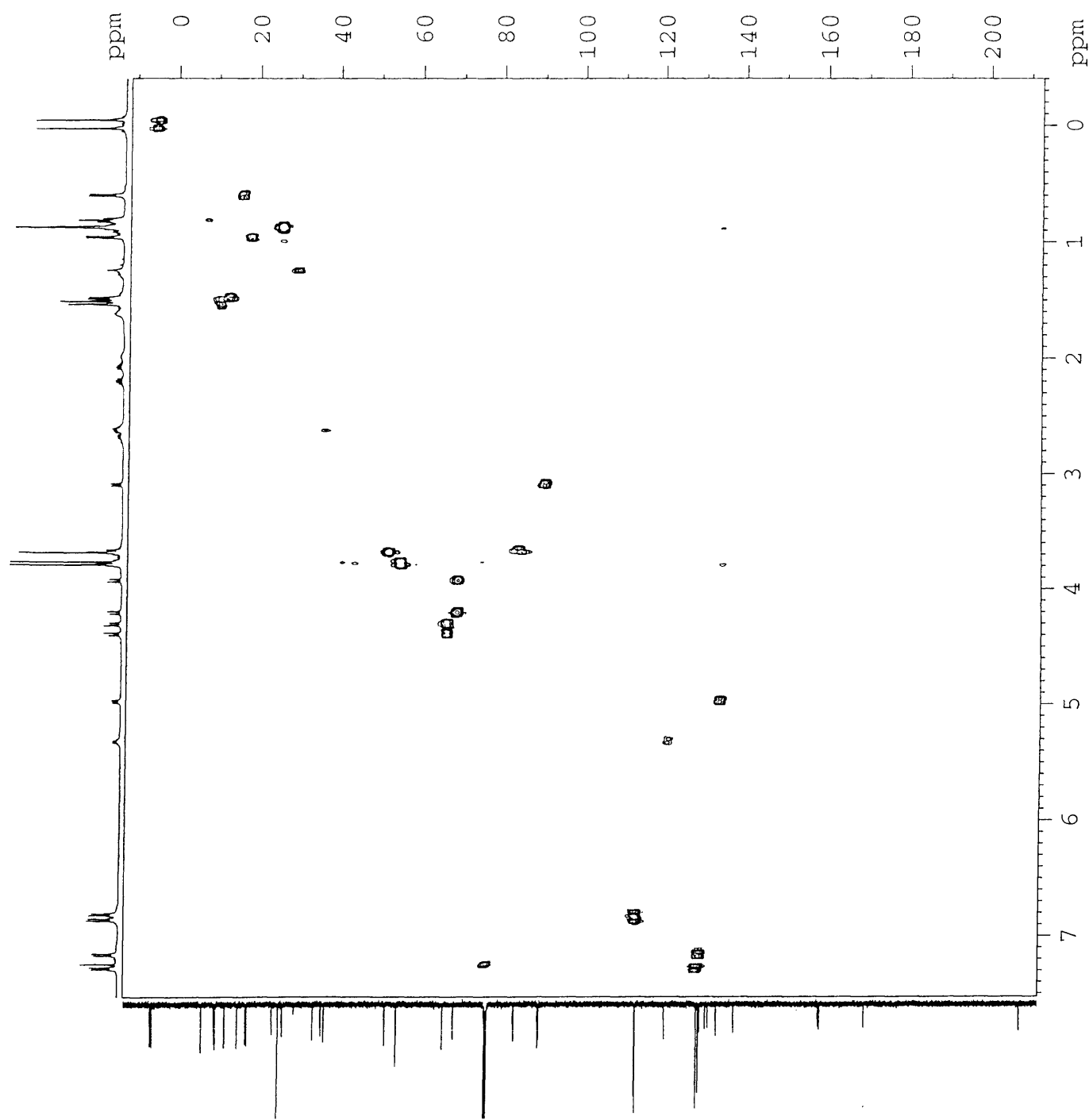
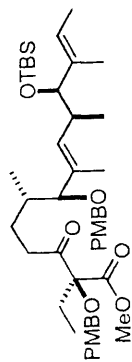
III-JG-188  
DEPT  
CDCl<sub>3</sub>

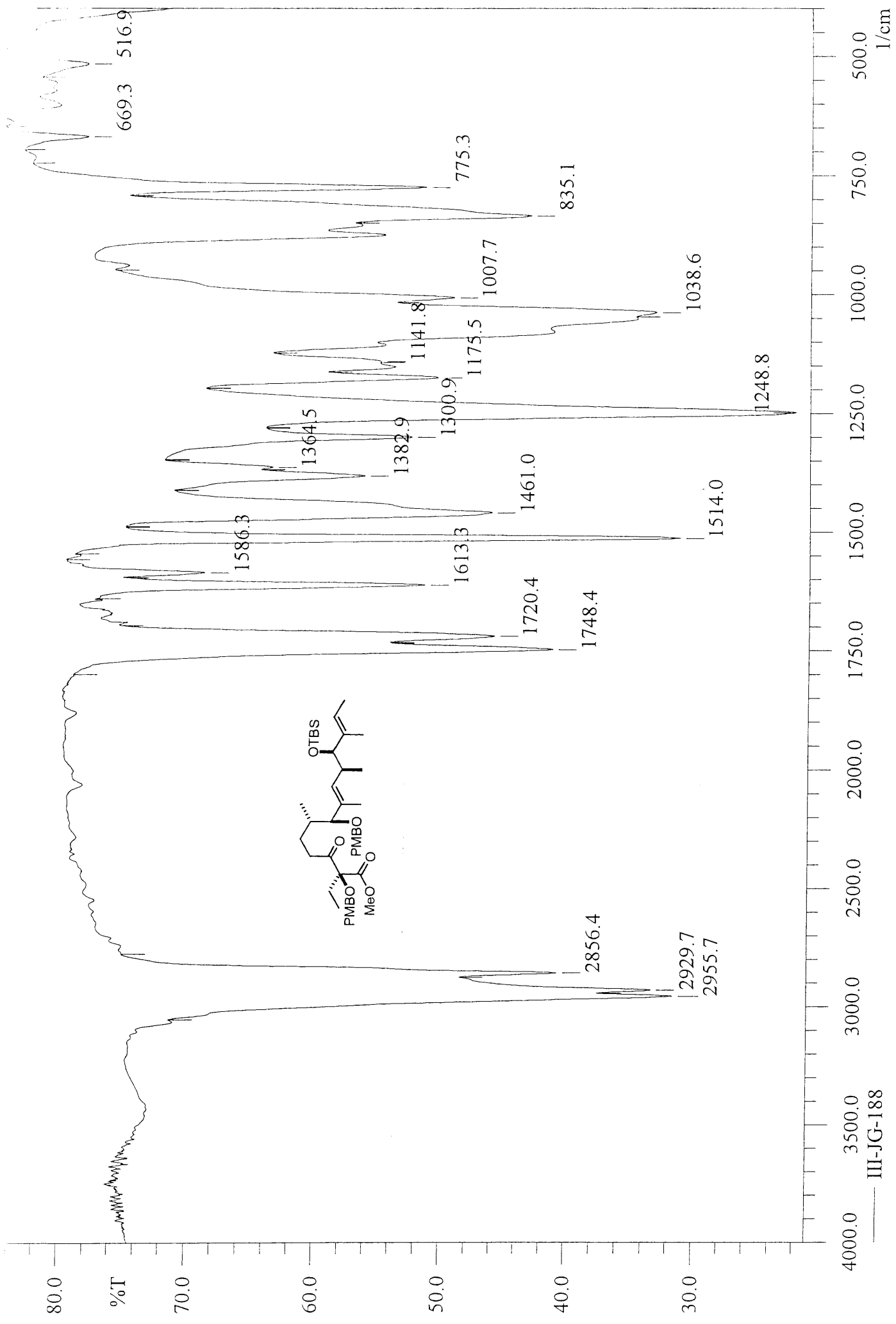


III-JG-188  
COSY  
CDCl<sub>3</sub>

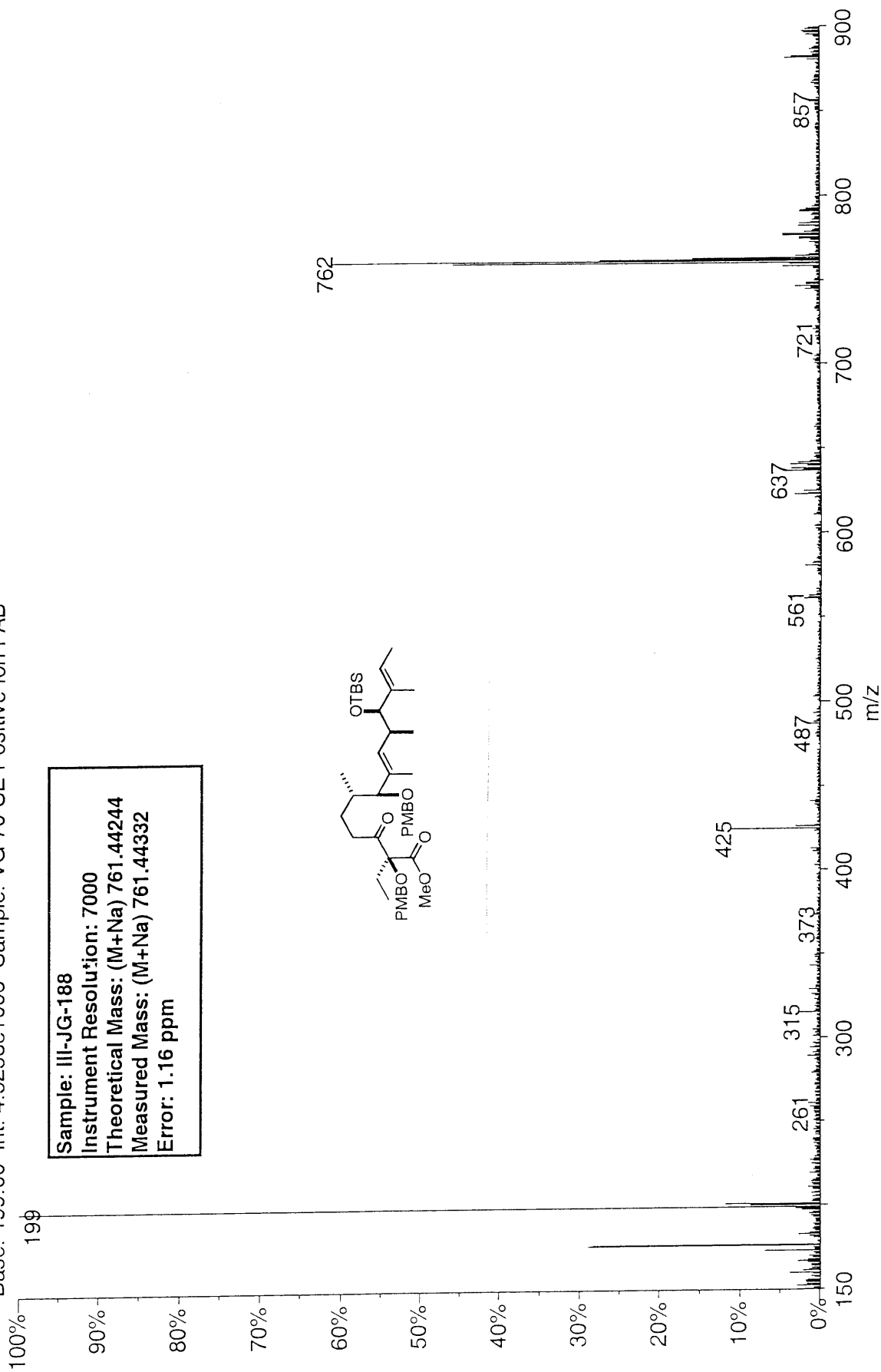


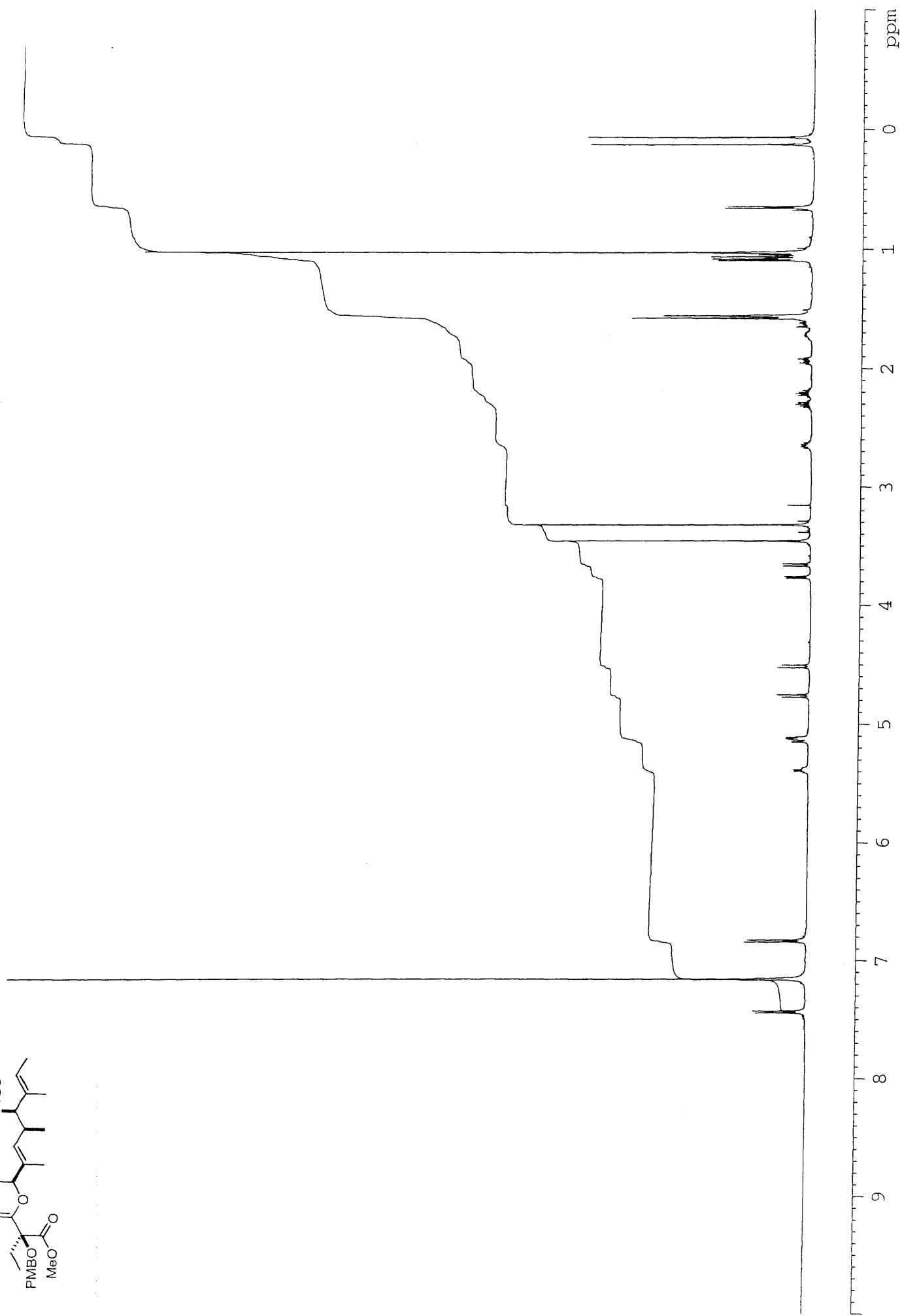
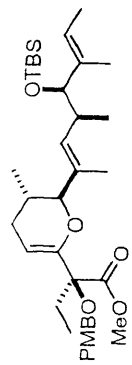
III-JG-188  
HMQC  
CDCl<sub>3</sub>

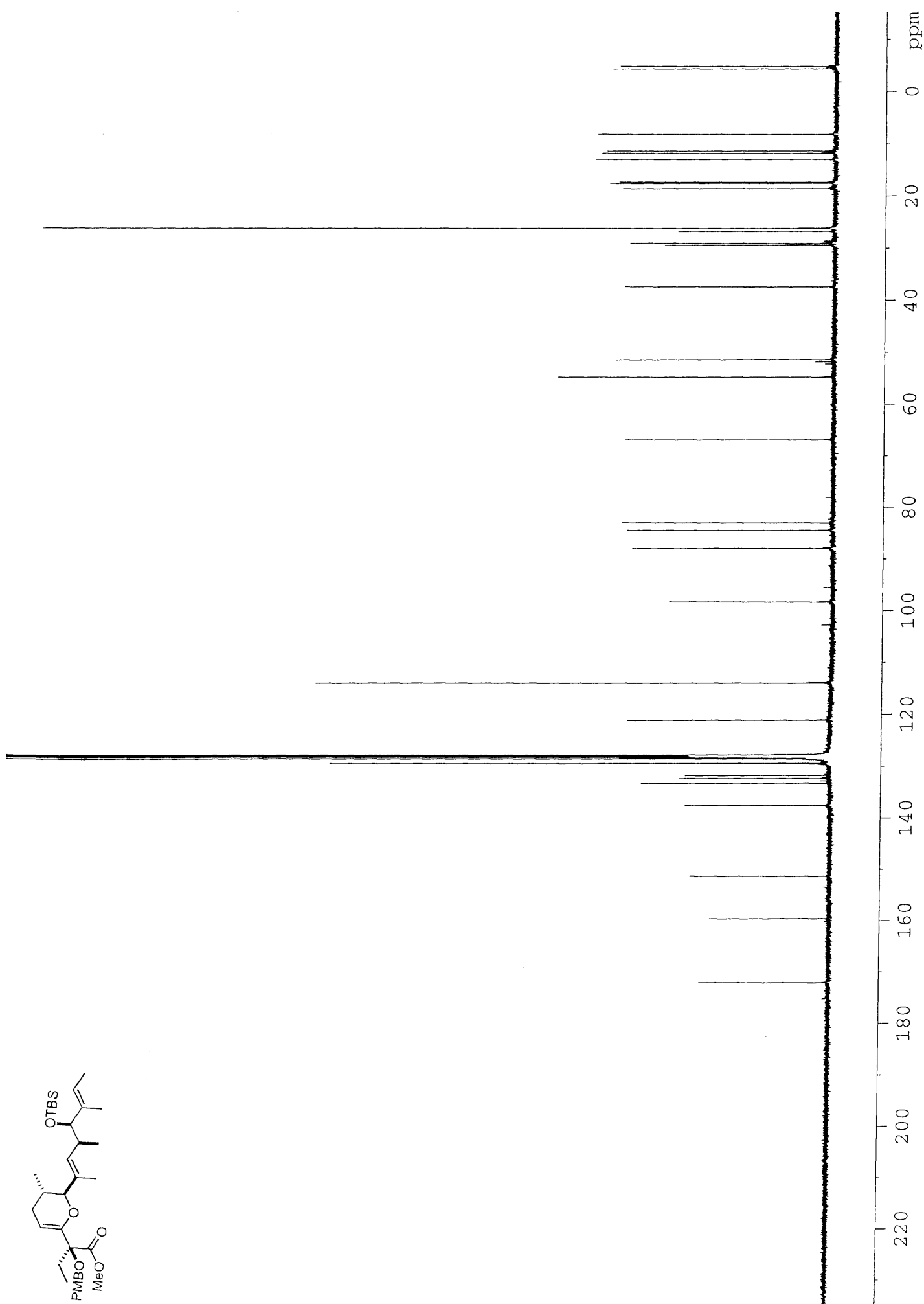
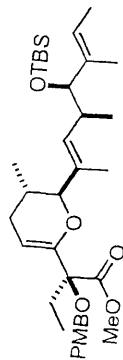


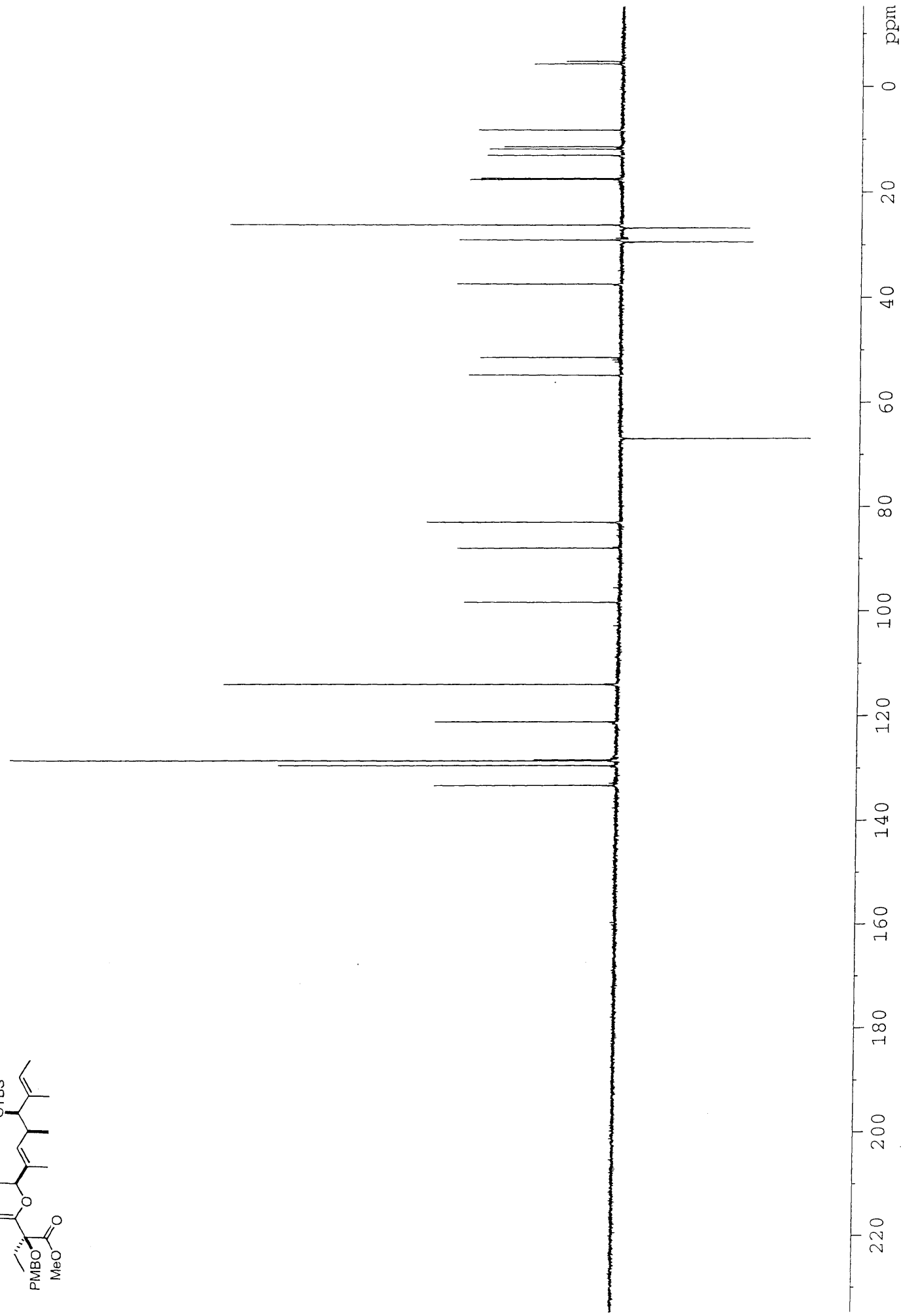
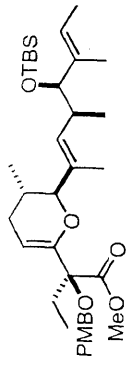


01051005: Scan Avg 191-192 (34.97 - 35.15 min) - Back  
Base: 199.00 Int: 4.5258e+006 Sample: VG 70-SE Positive Ion FAB

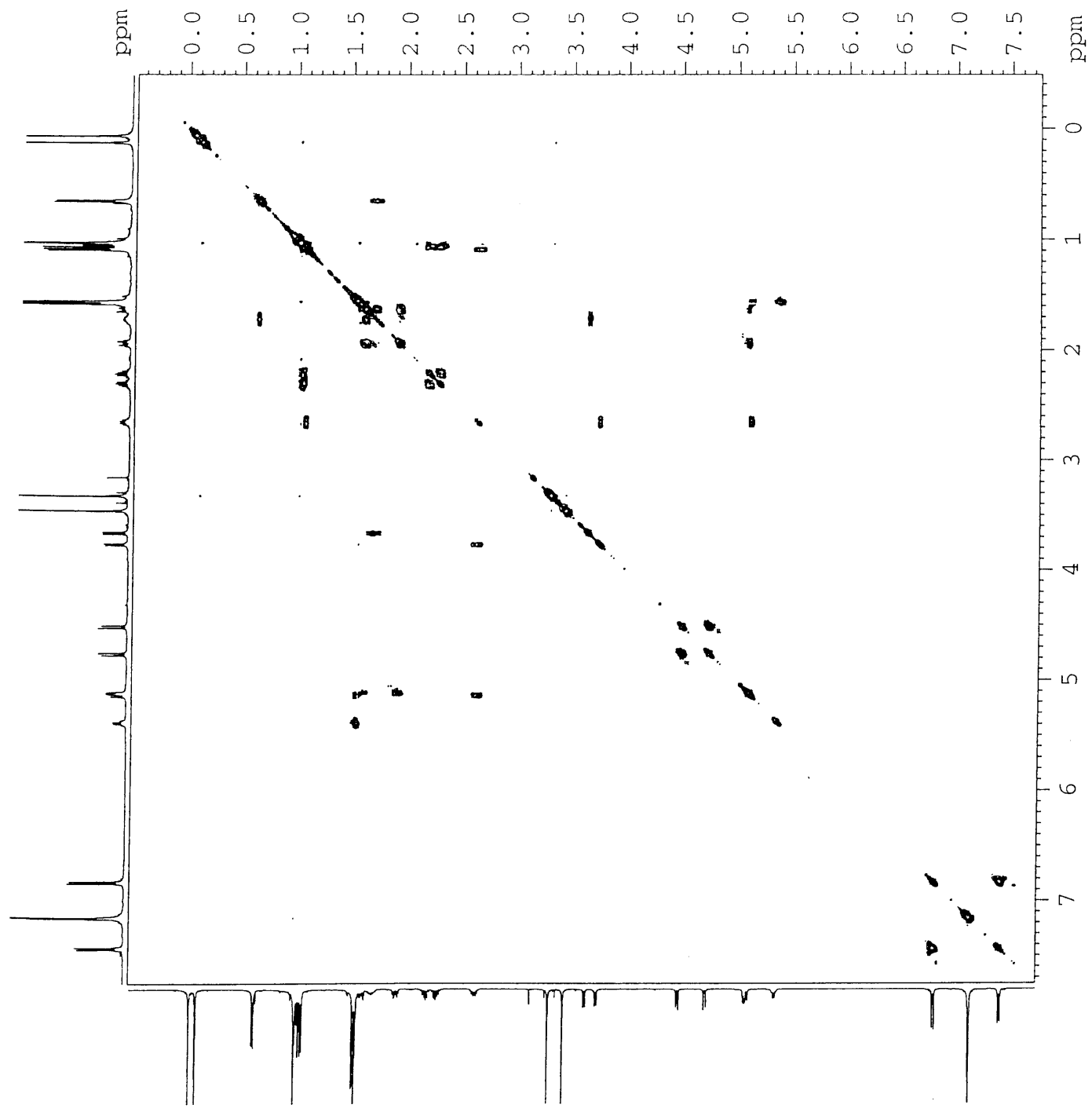
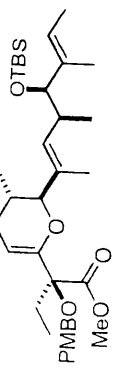


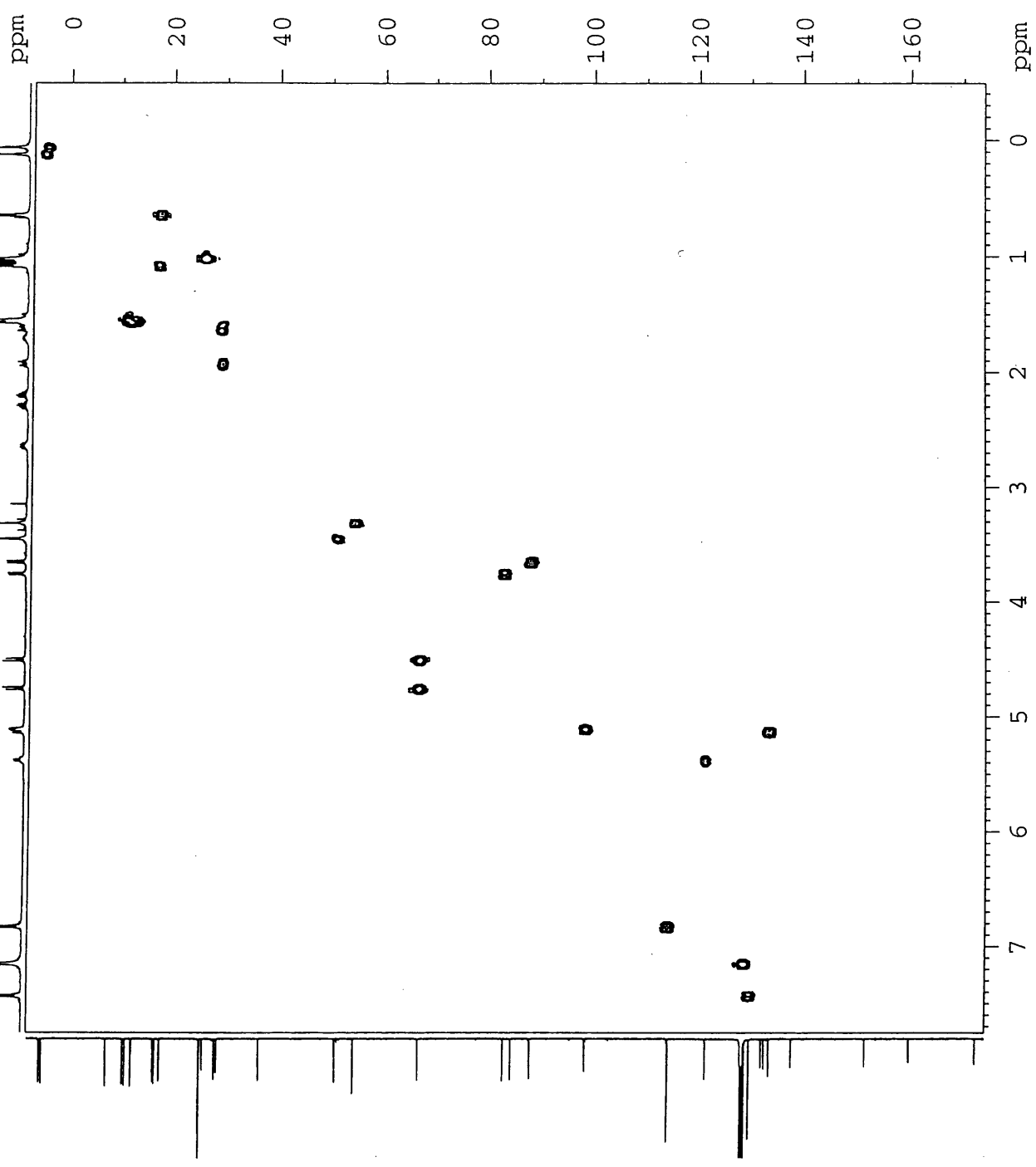
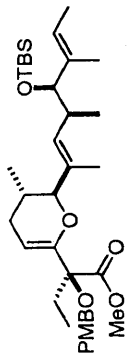


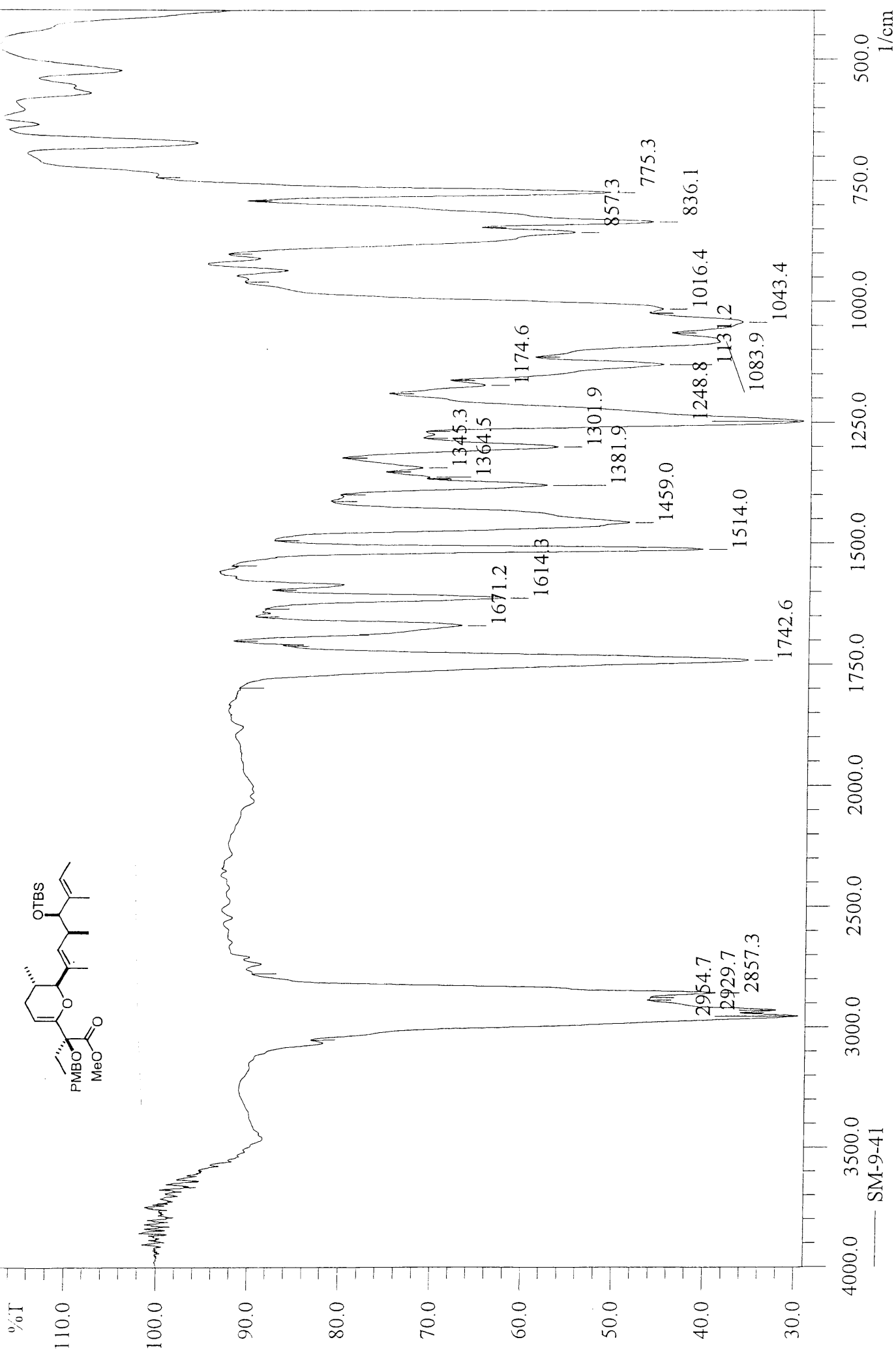
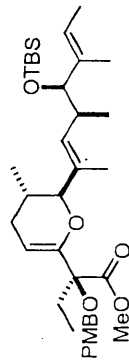










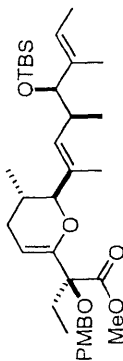
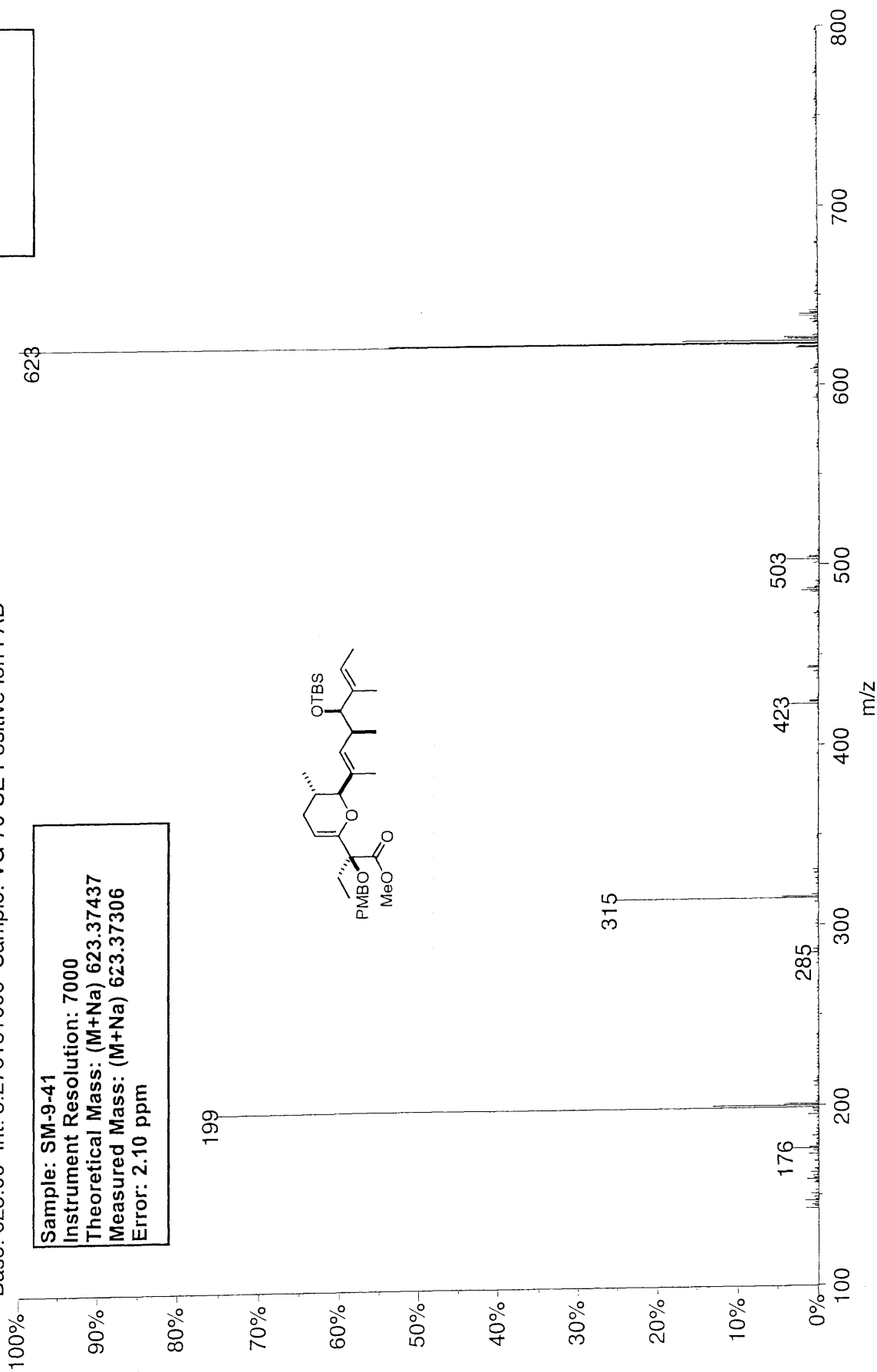


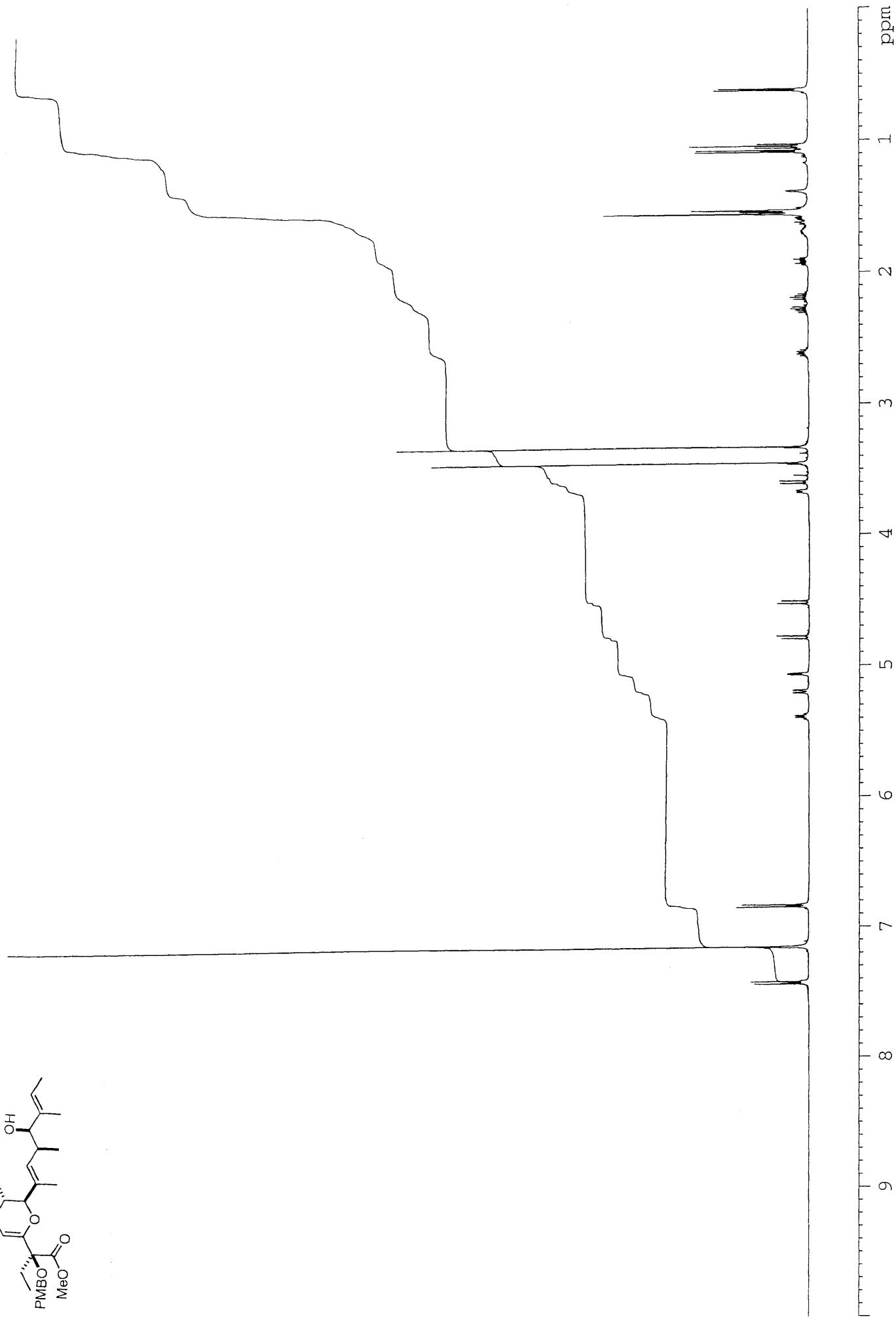
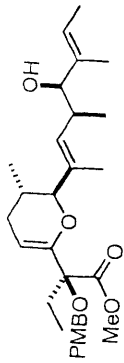
SM-9-41

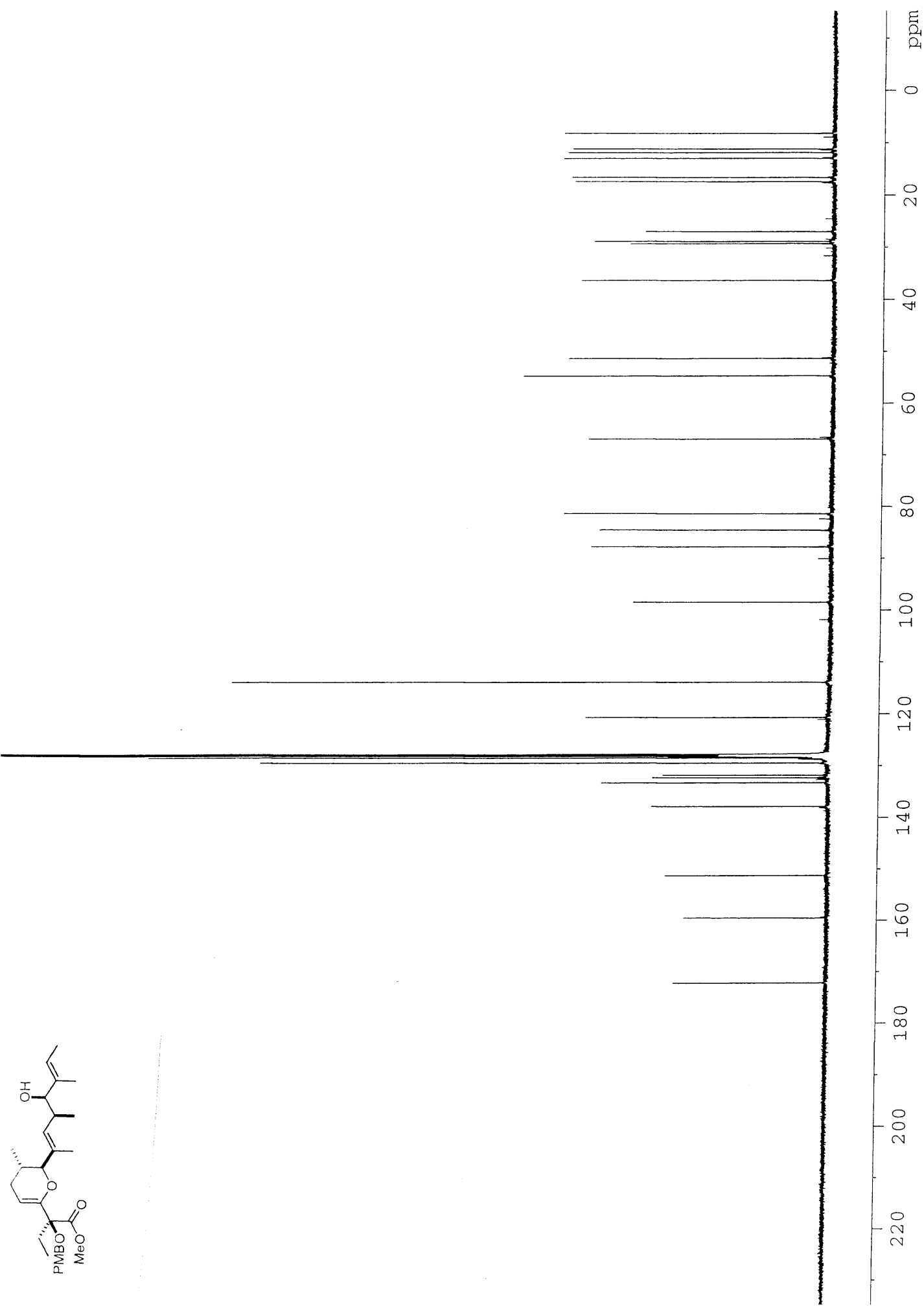
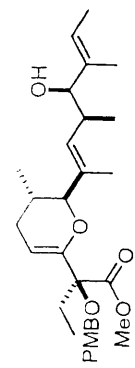
03270905: Scan Avg 141-142 (25.80 - 25.98 min) - Back  
Base: 623.00 Int: 3.2761e+006 Sample: VG 70-SE Positive Ion FAB

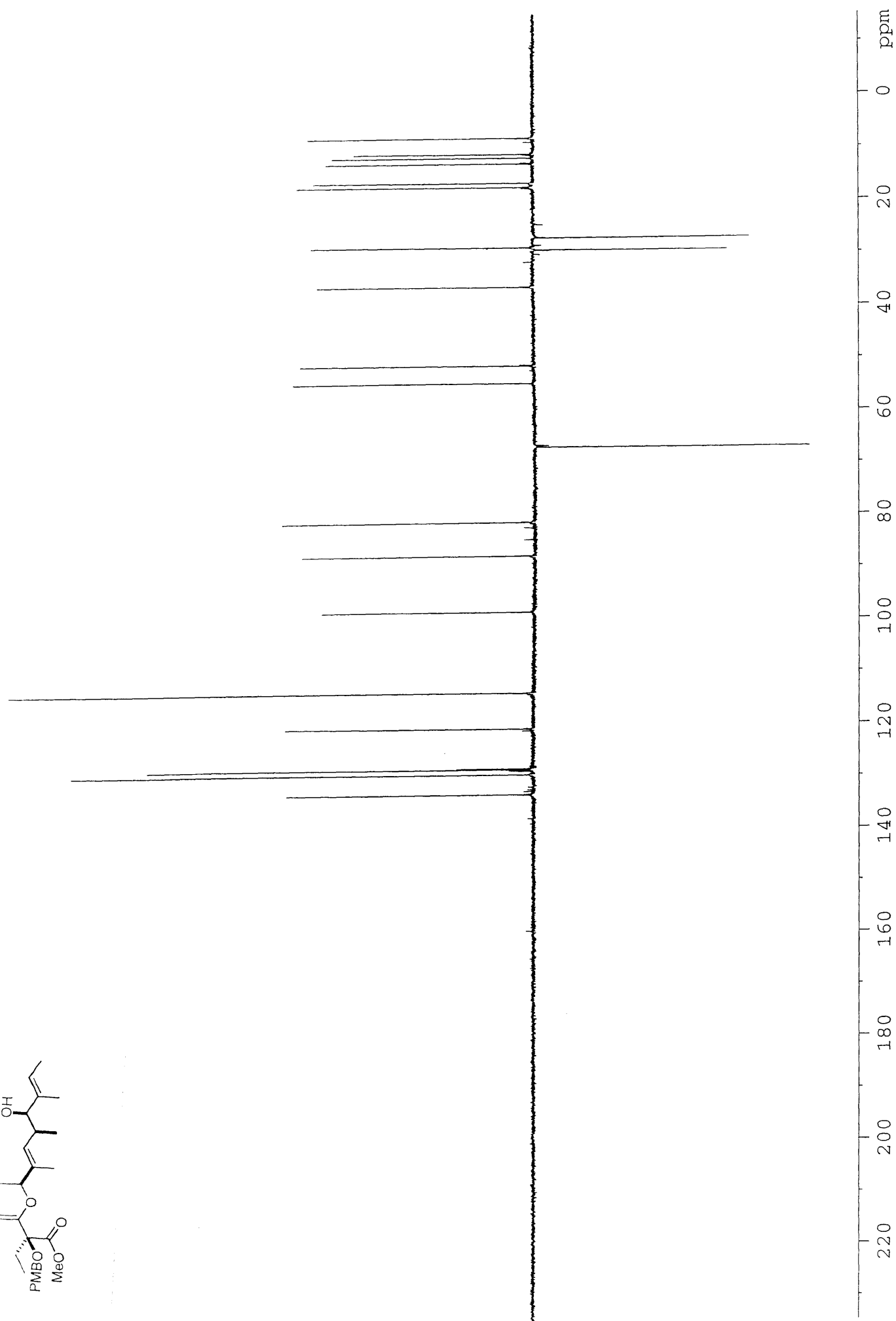
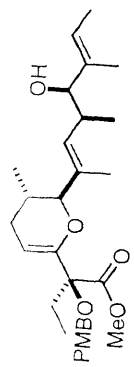
sm-9-41

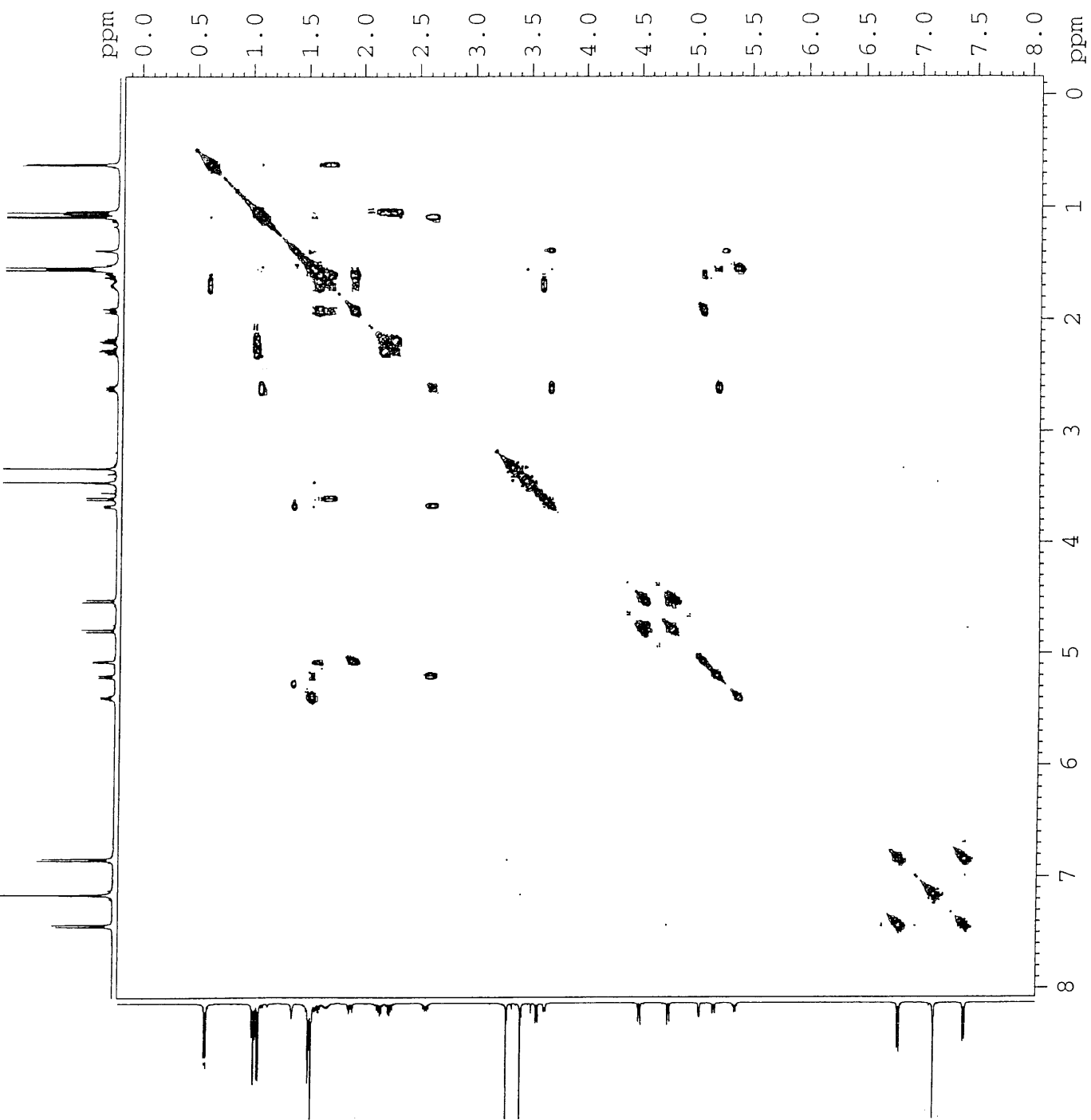
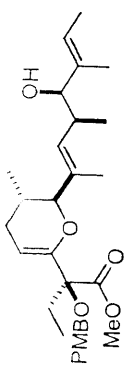
Sample: SM-9-41  
Instrument Resolution: 7000  
Theoretical Mass: (M+Na) 623.37437  
Measured Mass: (M+Na) 623.37306  
Error: 2.10 ppm



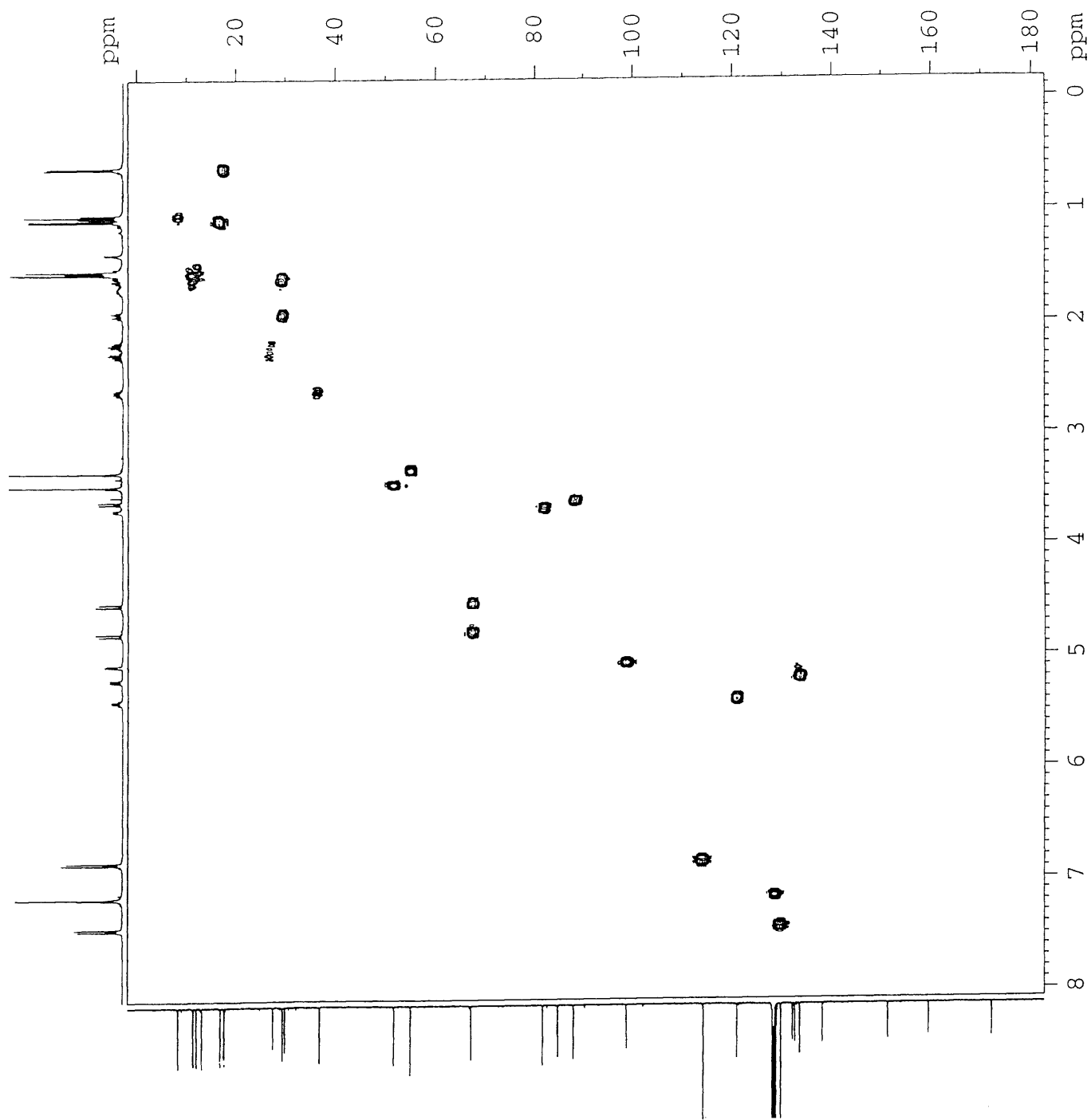
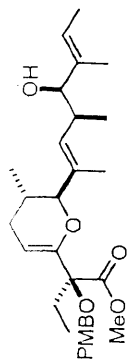


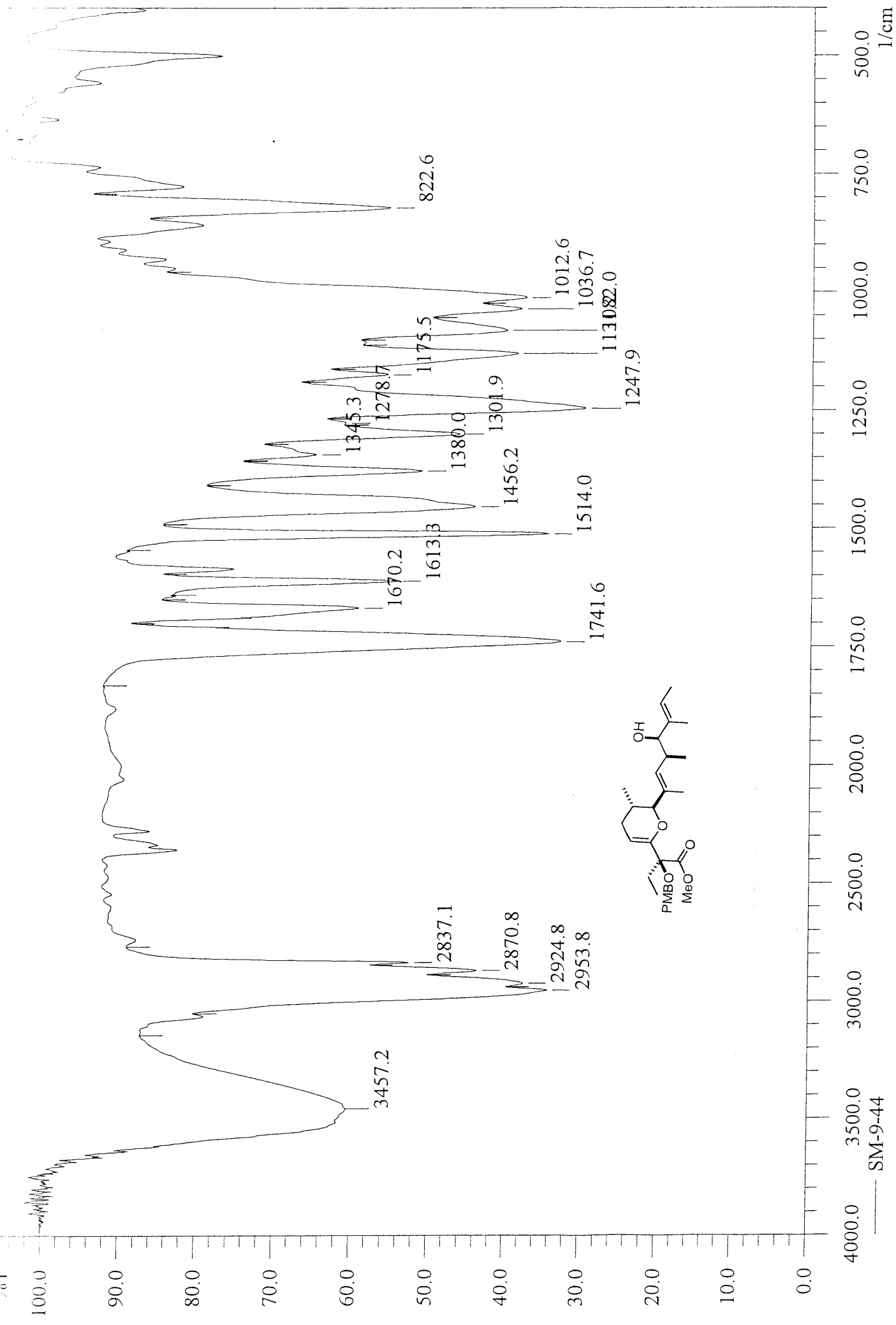






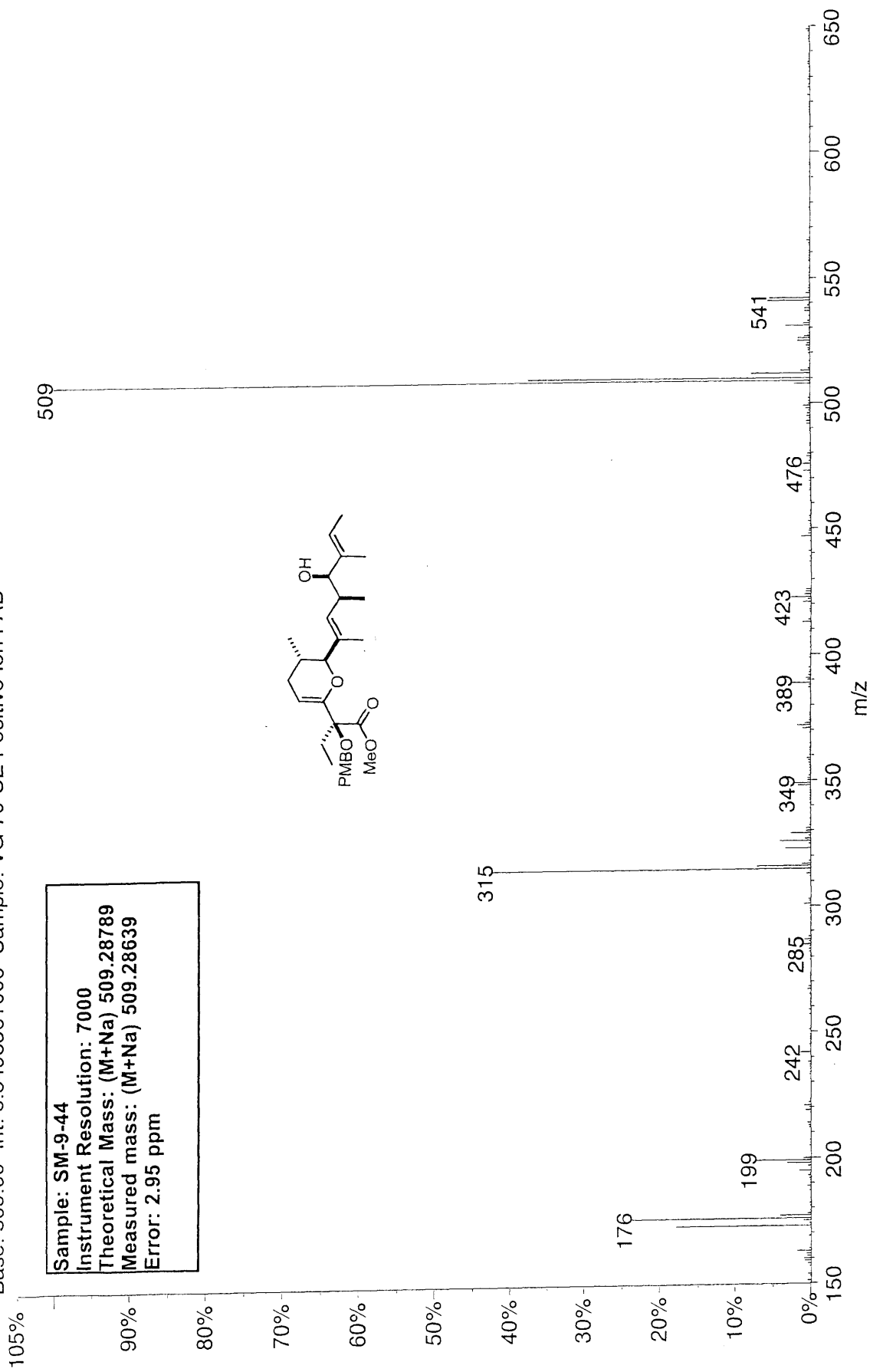


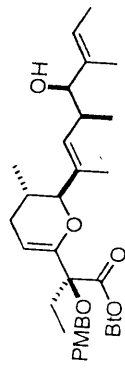




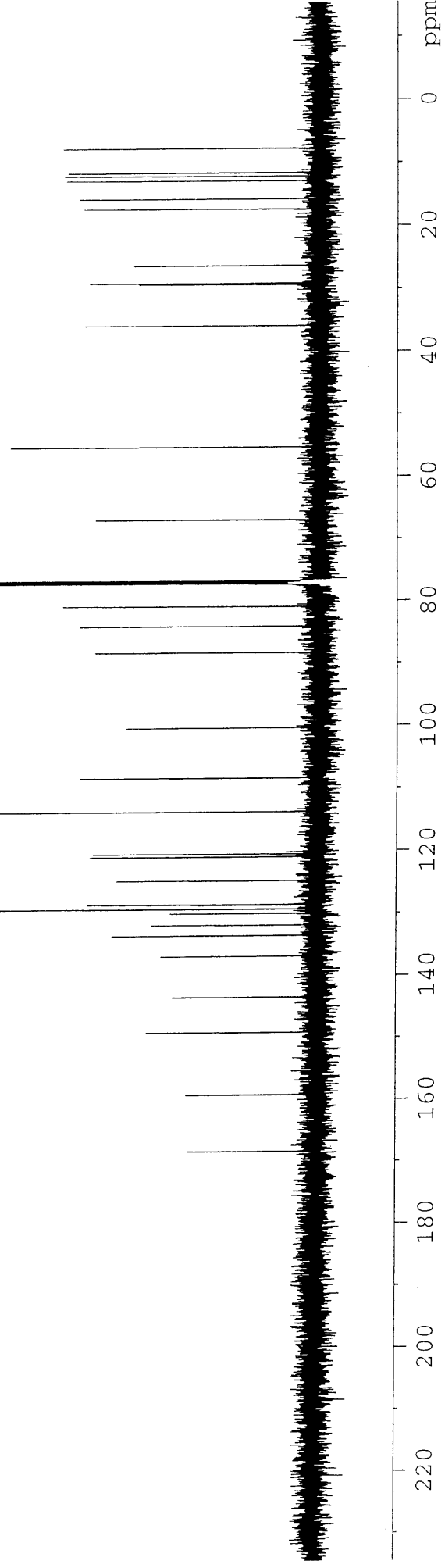
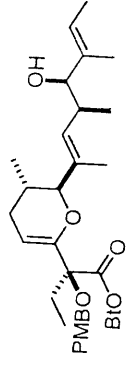
04121005: Scan 153 (28.00 min) - Back  
Base: 509.00 Int: 6.54983e+006 Sample: VG 70-SE Positive Ion FAB

Sample: SM-9-44  
Instrument Resolution: 7000  
Theoretical Mass: (M+Na) 509.28789  
Measured mass: (M+Na) 509.28639  
Error: 2.95 ppm

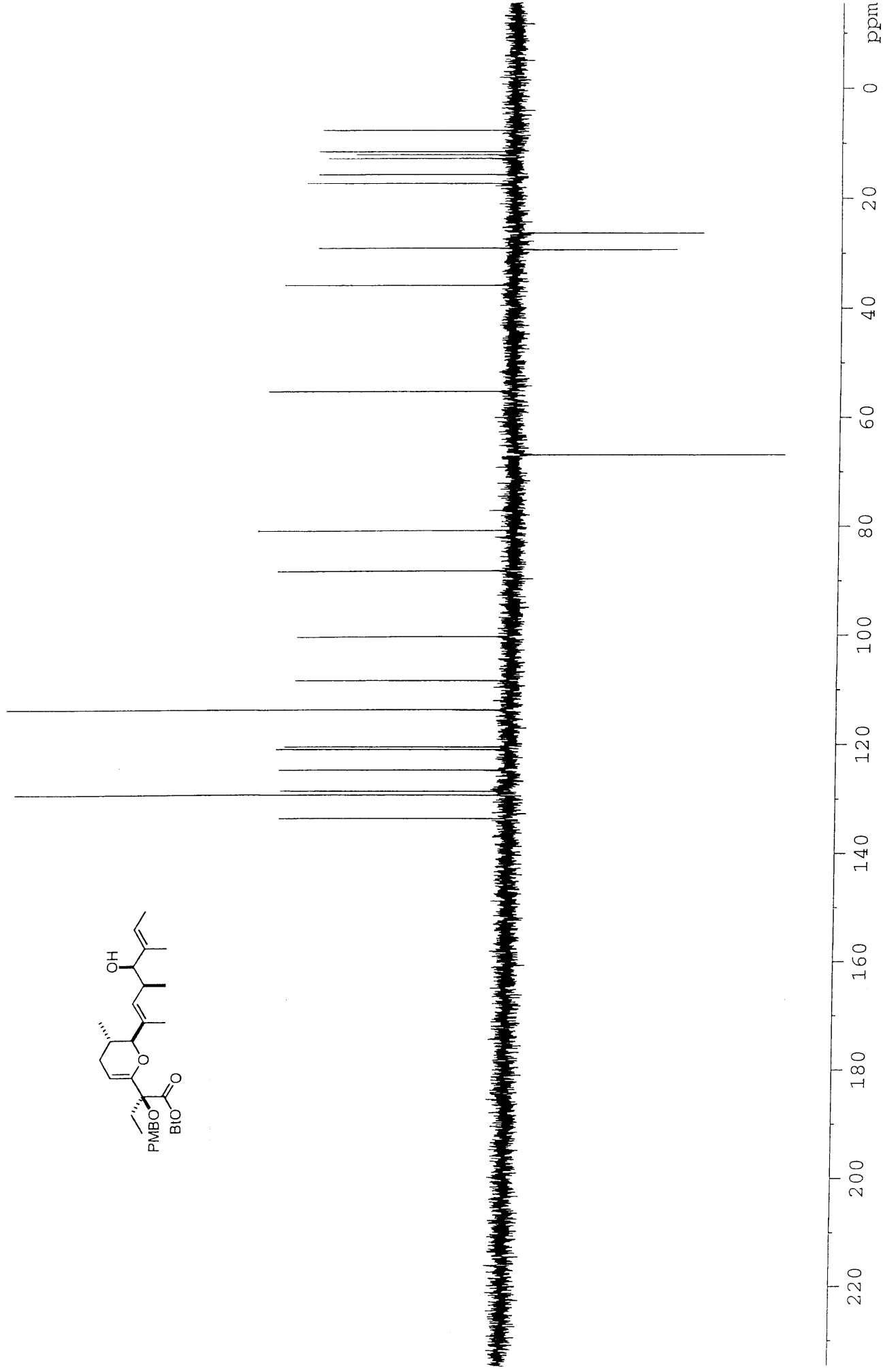
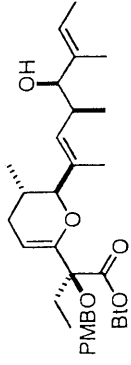




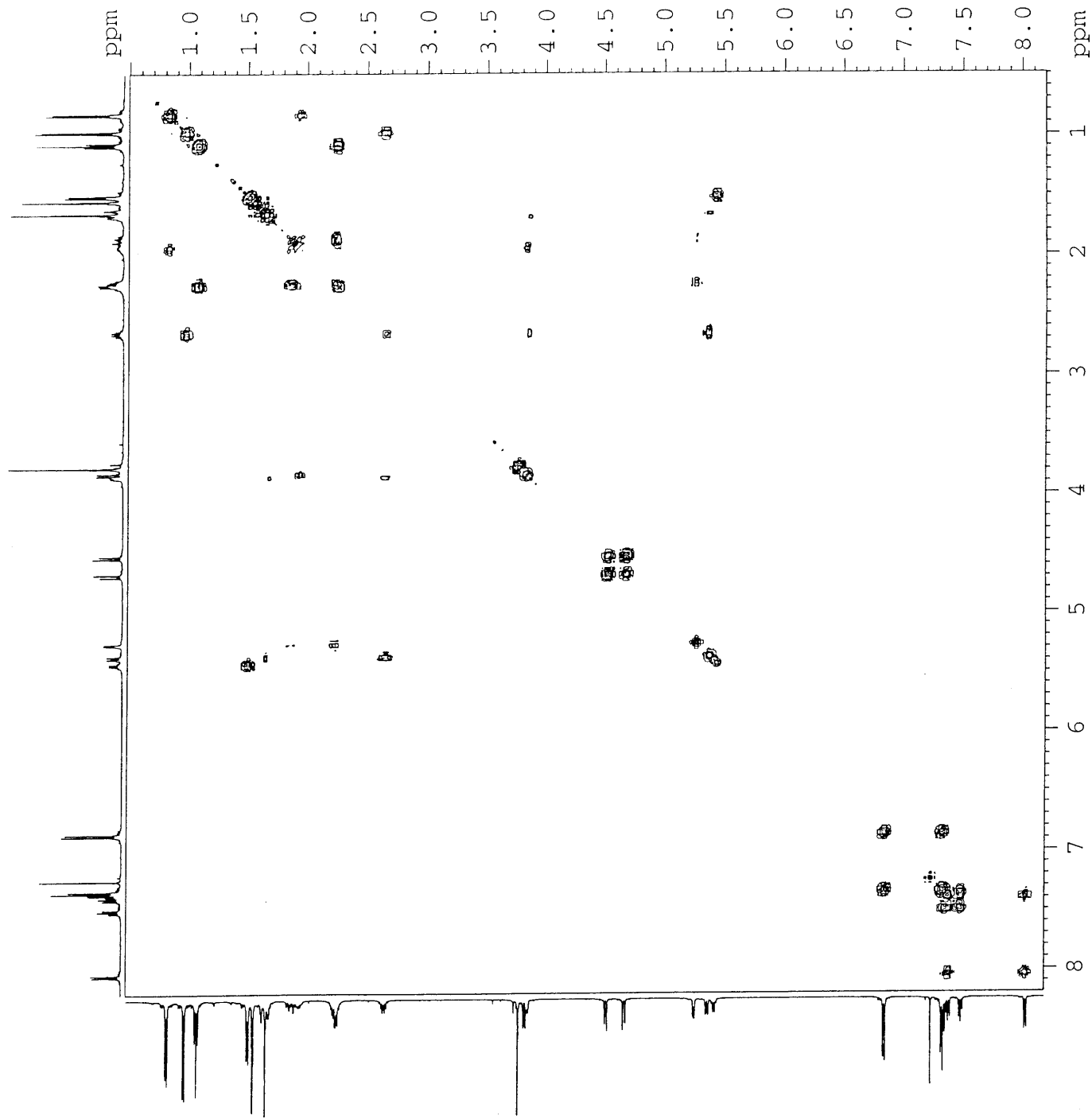
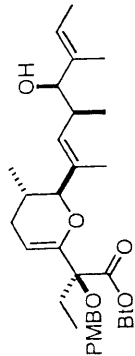
IV-JG-3  
CARBON  
CDC13

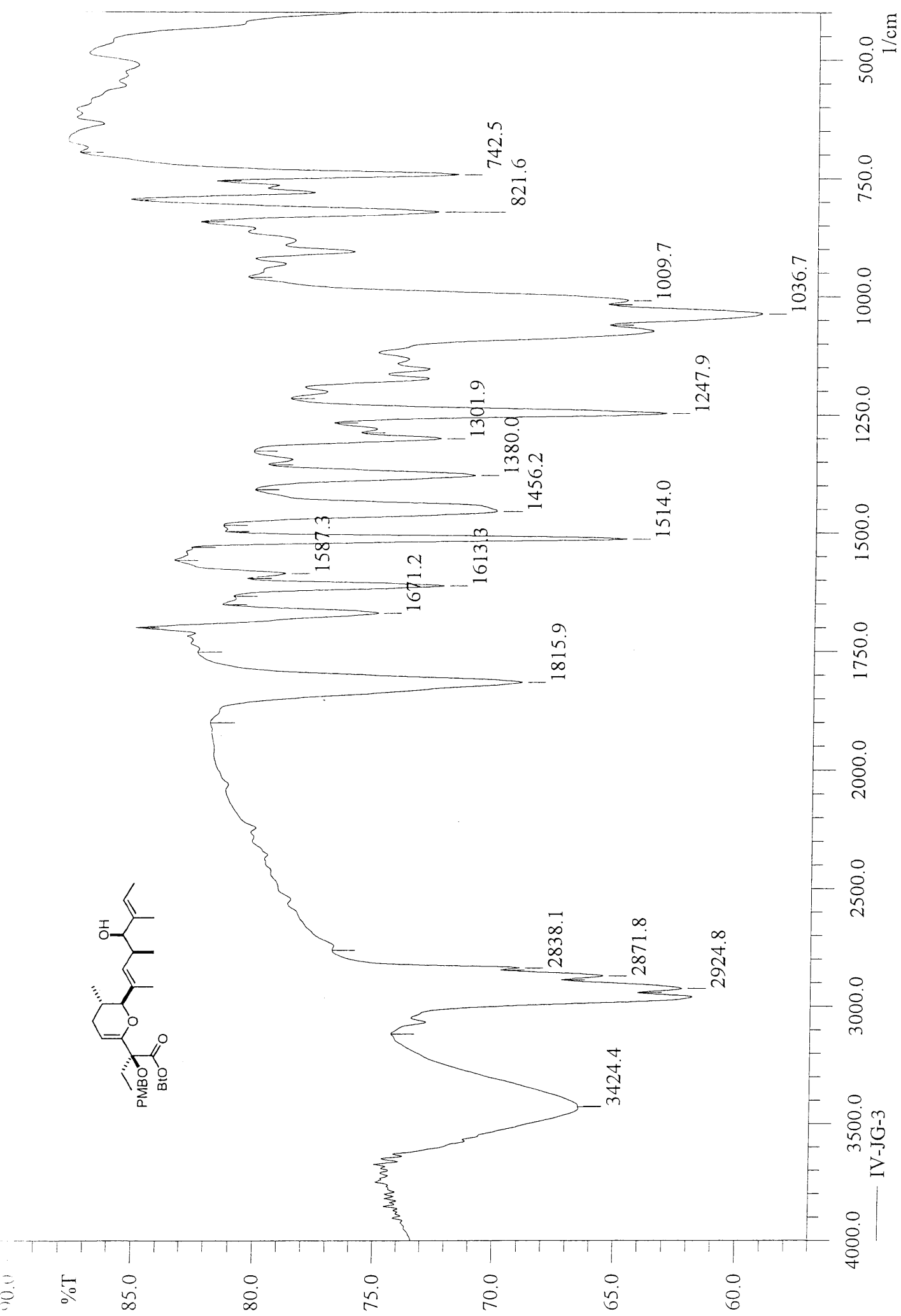


IV-JG-3  
DEPT  
CDC13



1V-JG-3  
COSY  
CDC13

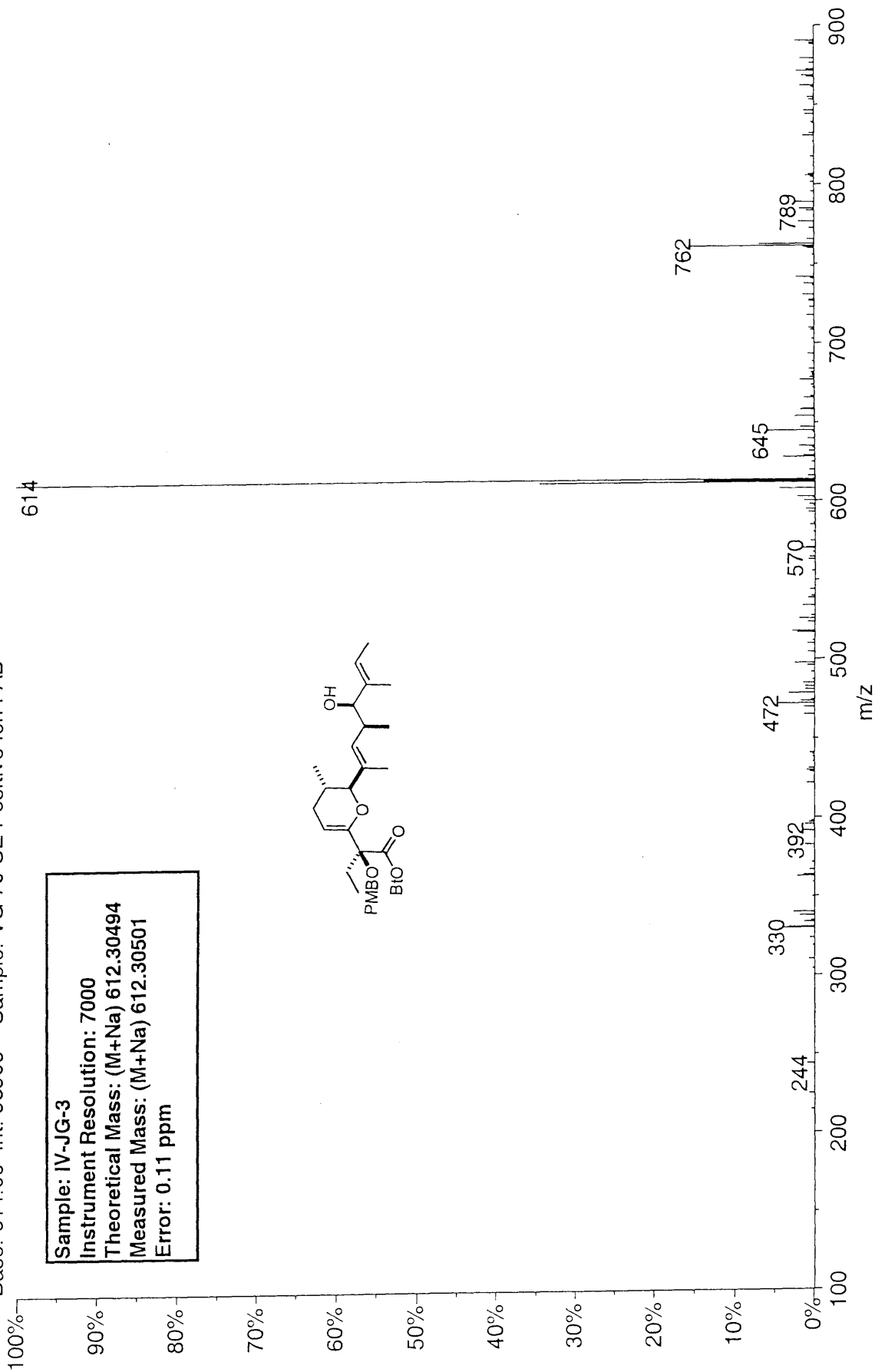
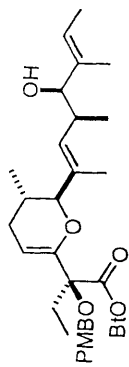




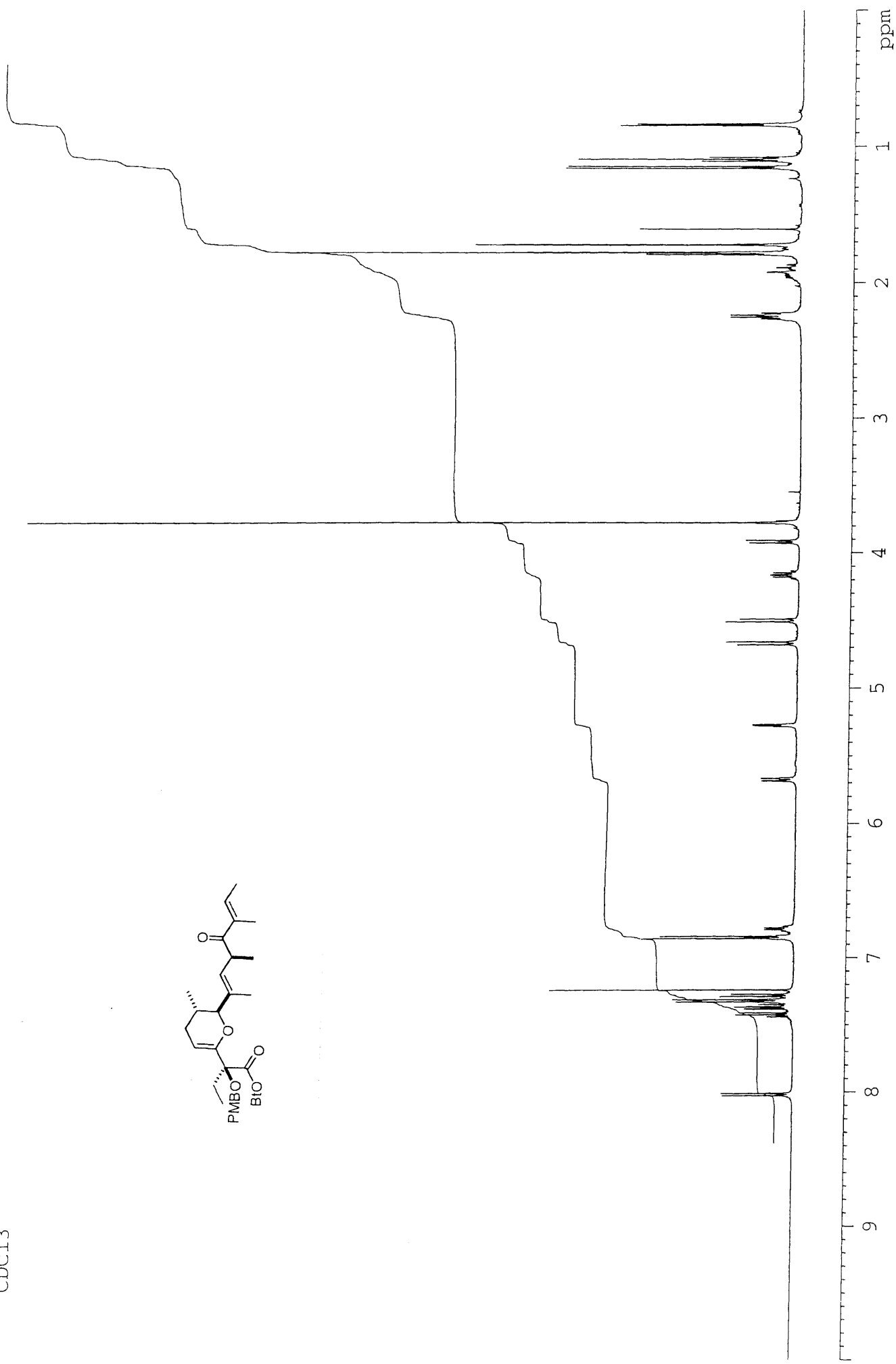
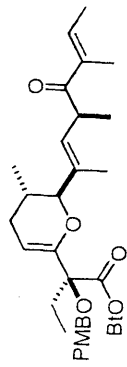


03270905; Scan Avg 155-157 (28.37 - 28.73 min) - Back  
Base: 614.00 Int: 98906 Sample: VG 70-SE Positive Ion FAB

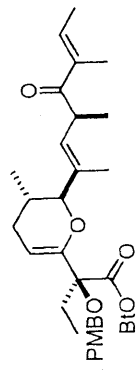
Sample: IV-JG-3  
Instrument Resolution: 7000  
Theoretical Mass: (M+Na) 612.30494  
Measured Mass: (M+Na) 612.30501  
Error: 0.11 ppm



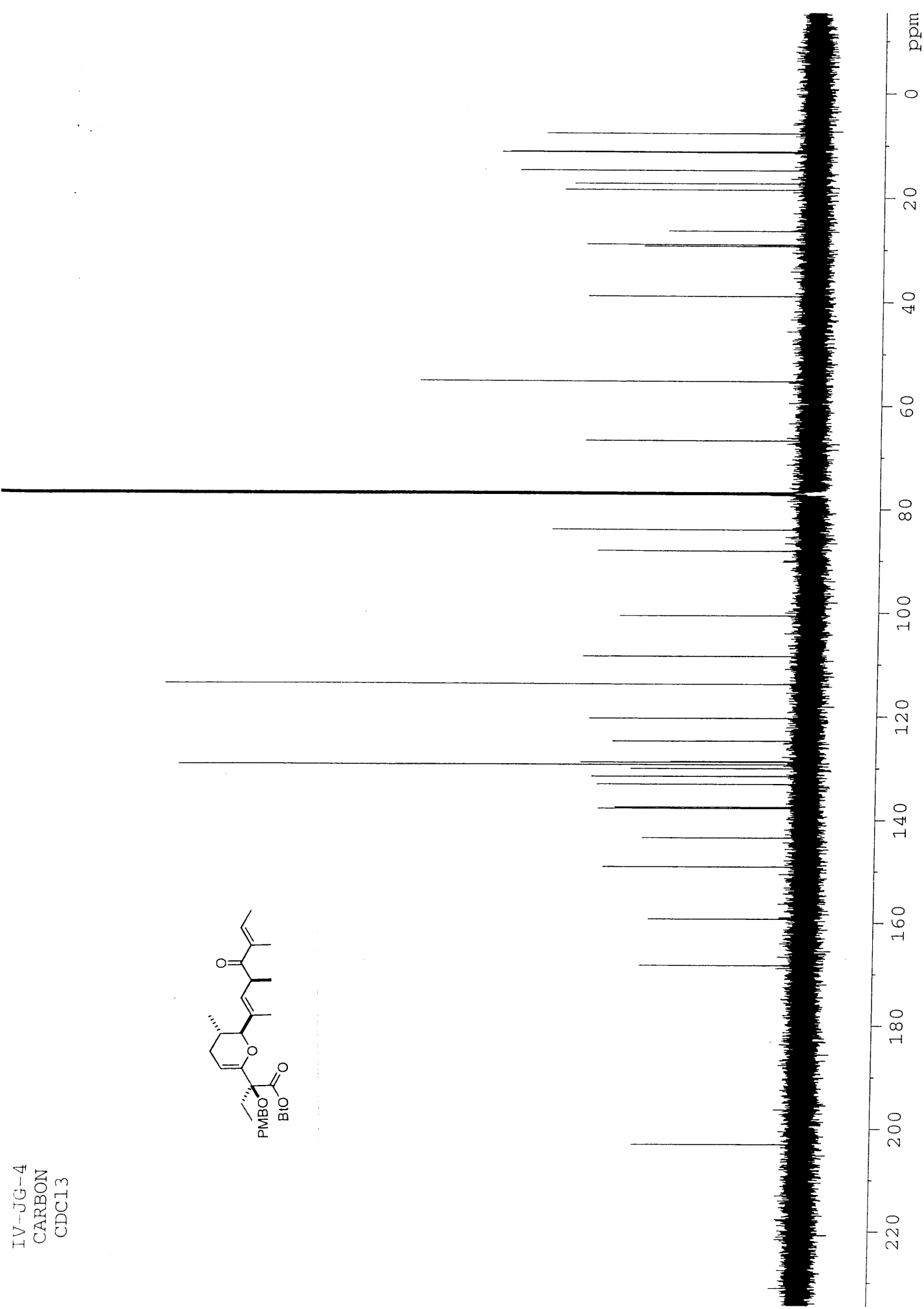
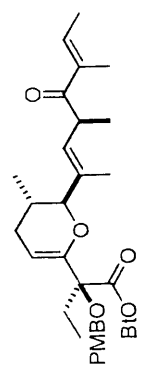
IV-JG-4  
PROTON  
CDCl3



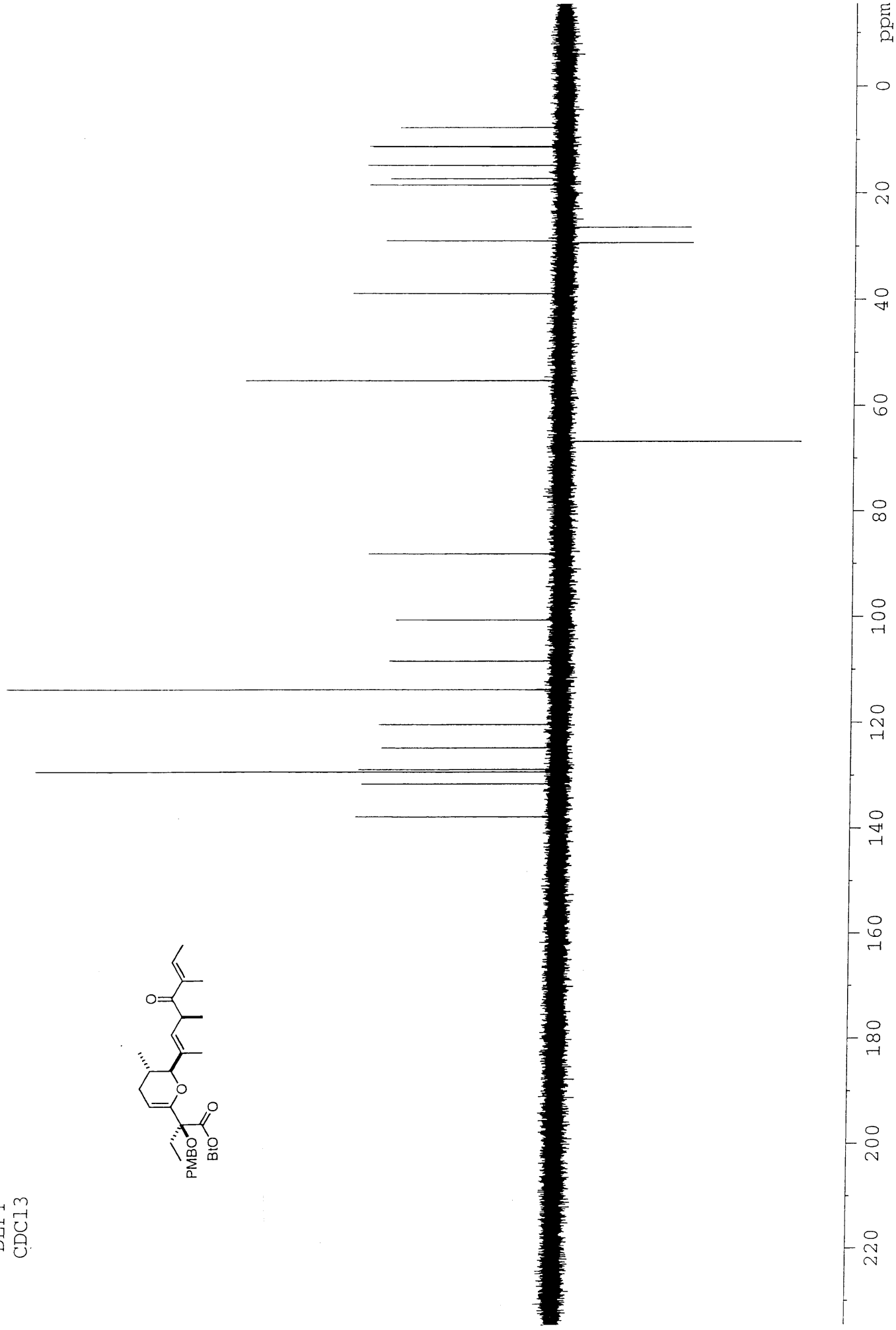
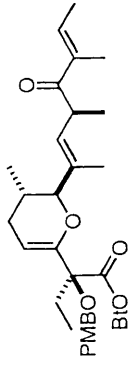
1V-JG-4  
PROTON  
CDCl3



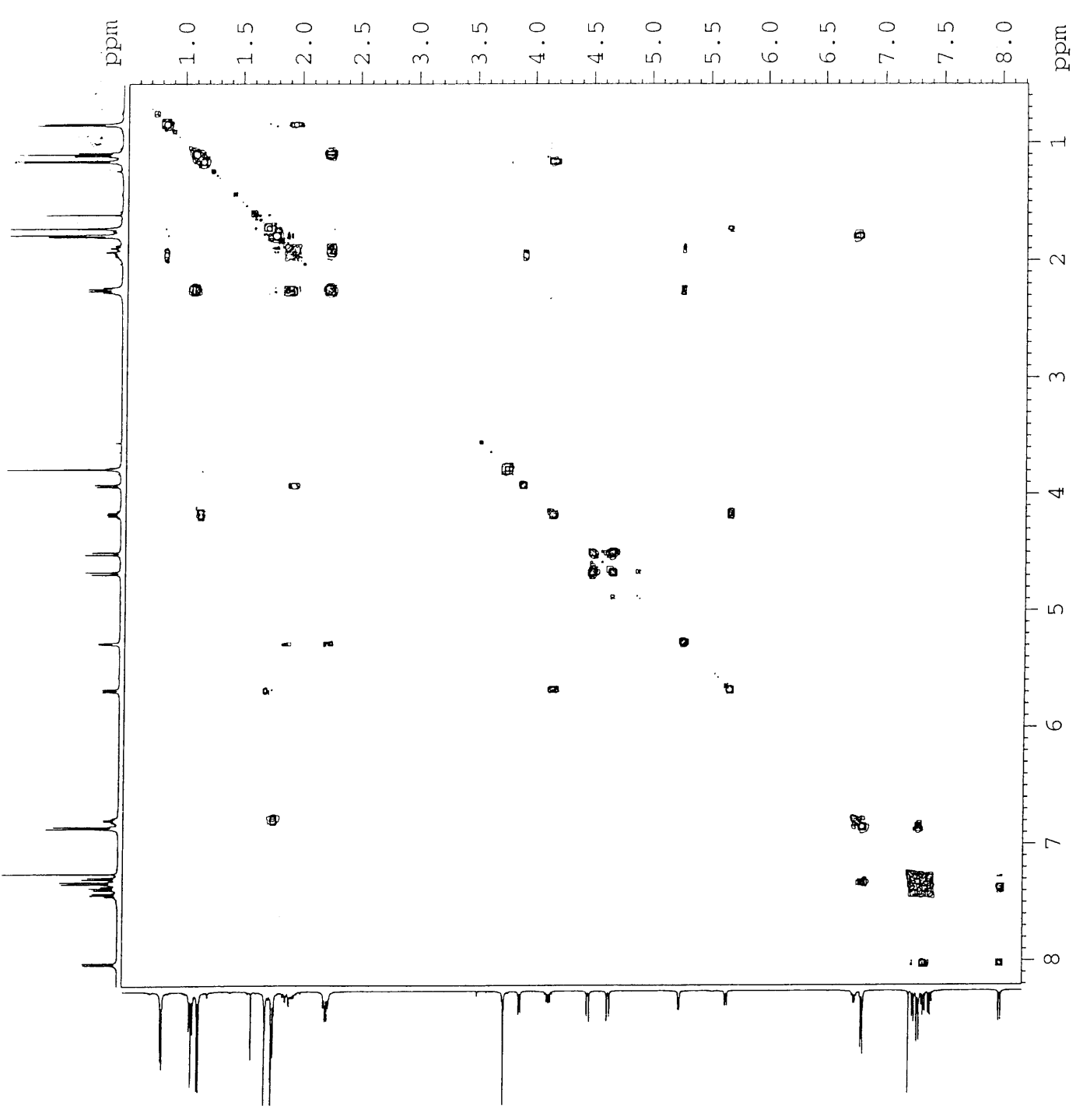
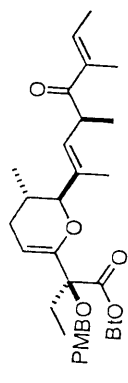
IV-JG-4  
CARBON  
CDCl3



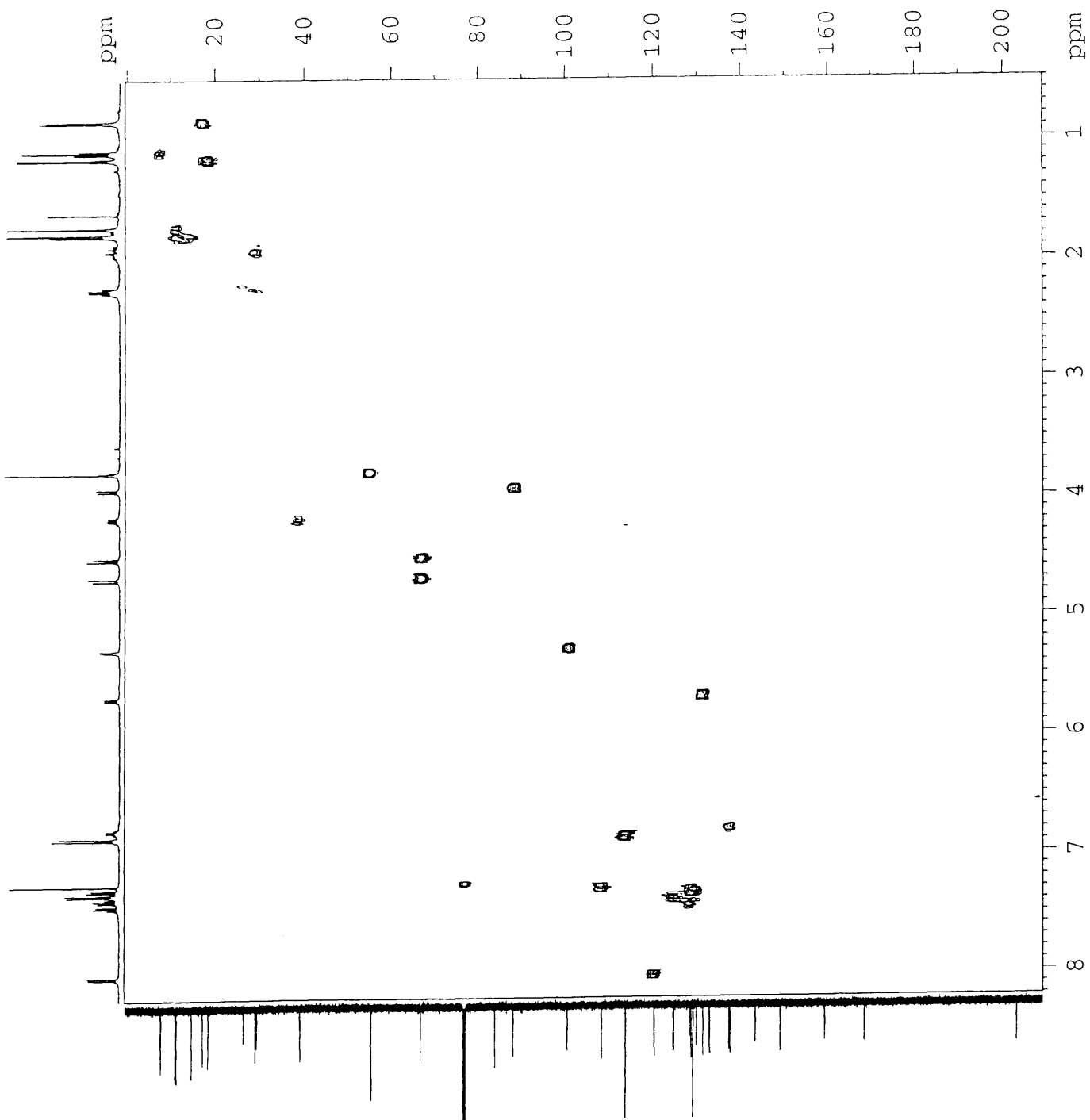
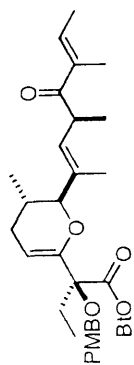
IV-JG-4  
DEPT  
CDCl<sub>3</sub>

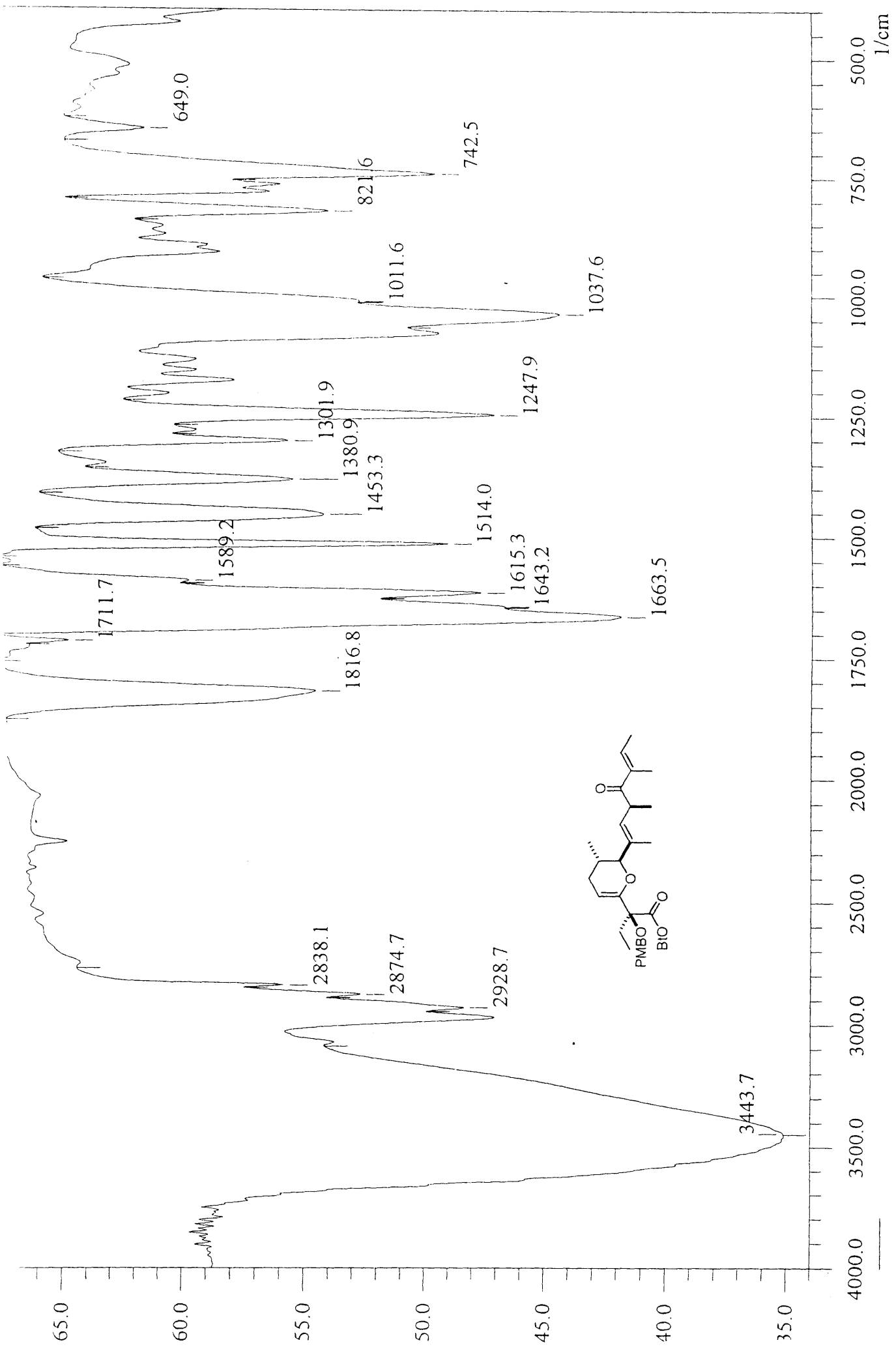


IV-JG-4  
COSY  
CDCl3



IV-JG-4  
 HMQC  
 CDCl<sub>3</sub>

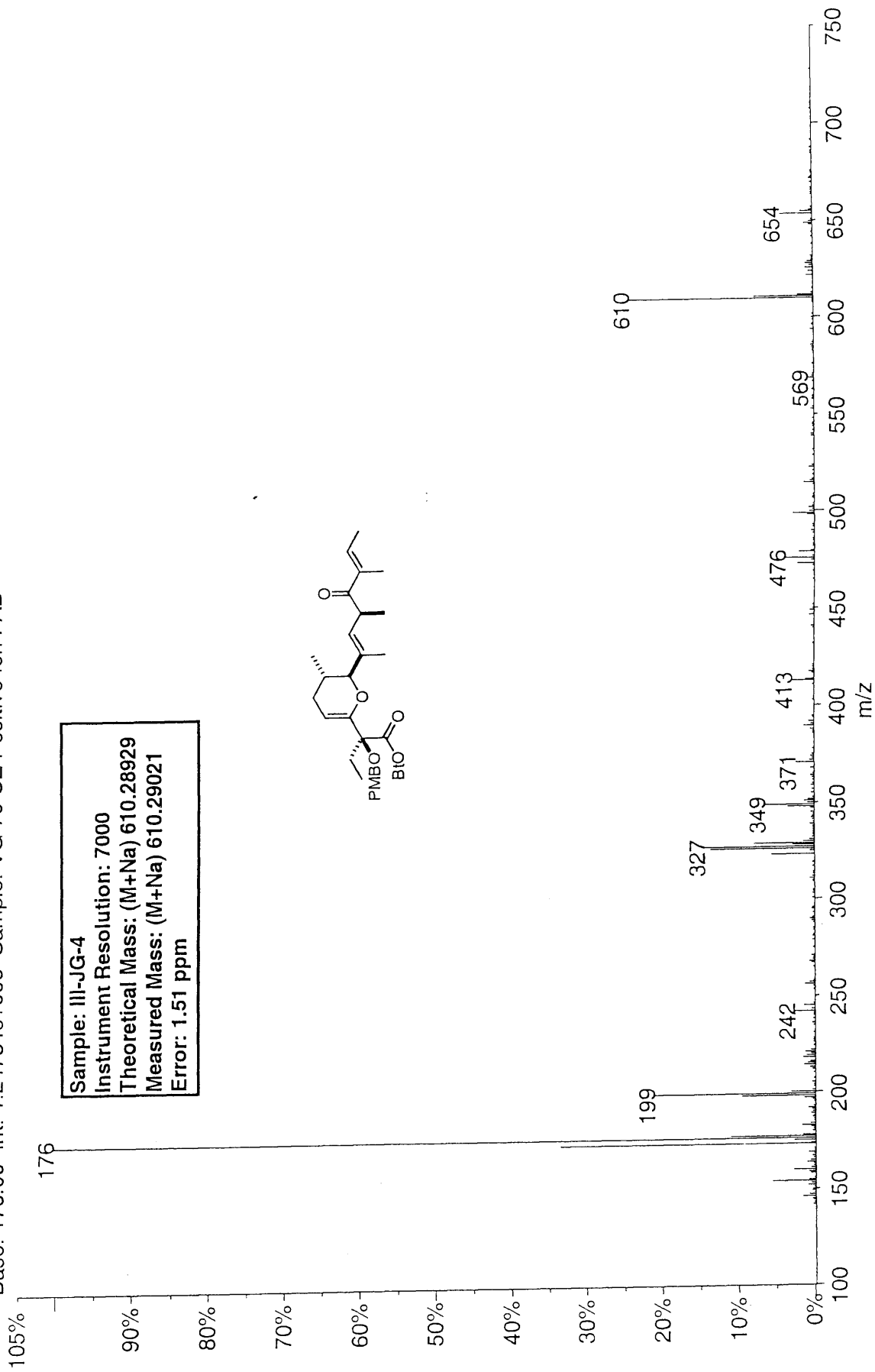
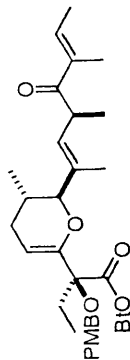






01161105: Scan Avg 13-15 (2.33 - 2.70 min) - Back  
Base: 176.00 Int: 1.24784e+006 Sample: VG 70-SE Positive Ion FAB

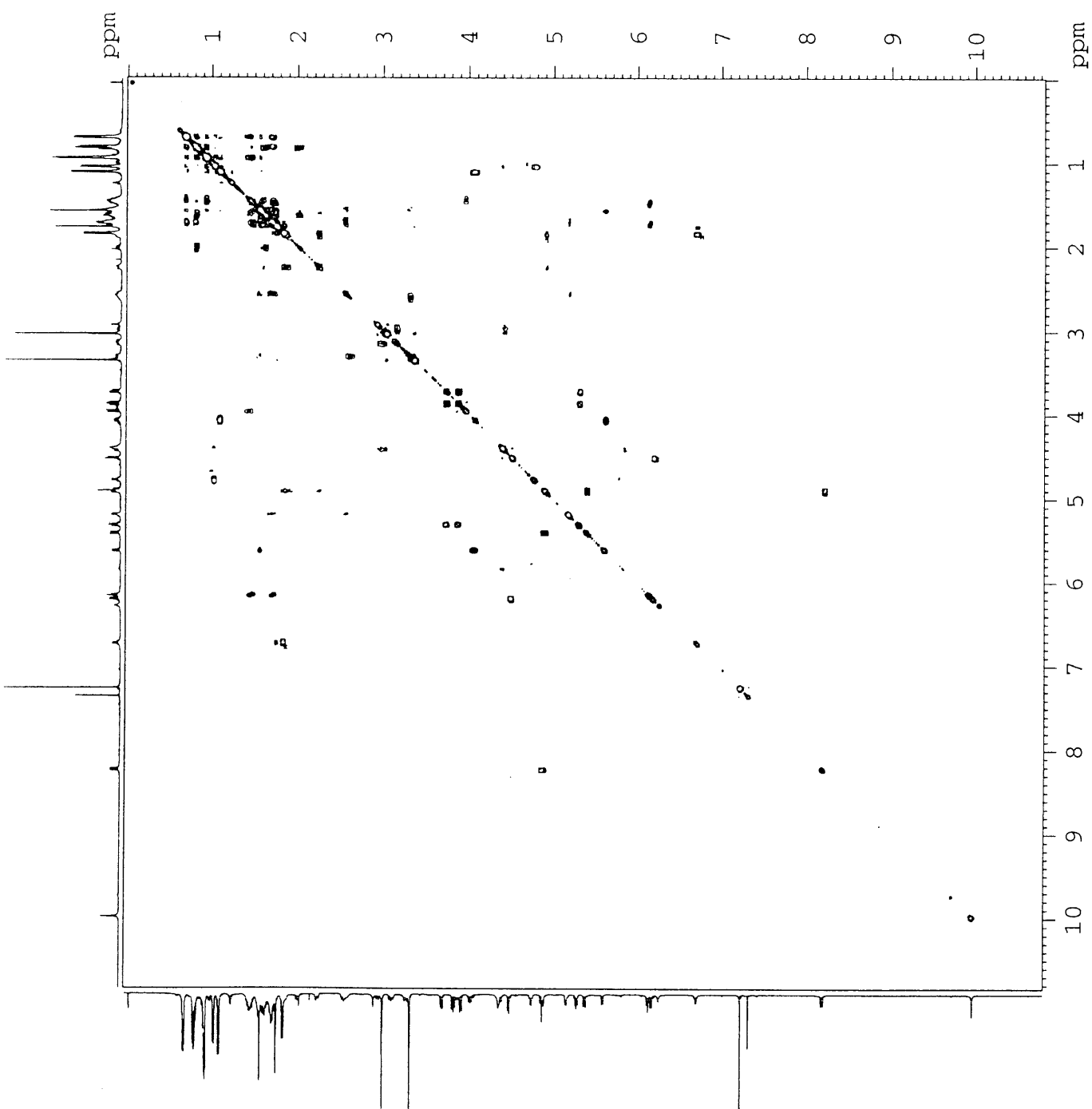
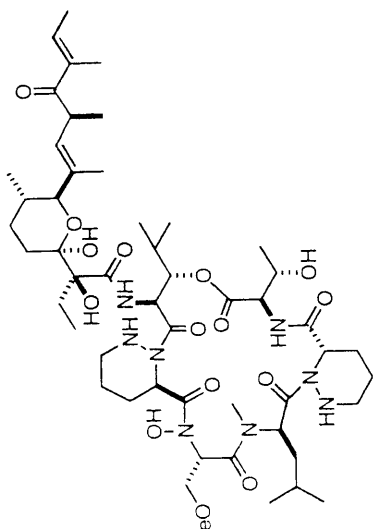
Sample: III-JG-4  
Instrument Resolution: 7000  
Theoretical Mass: (M+Na) 610.28929  
Measured Mass: (M+Na) 610.29021  
Error: 1.51 ppm

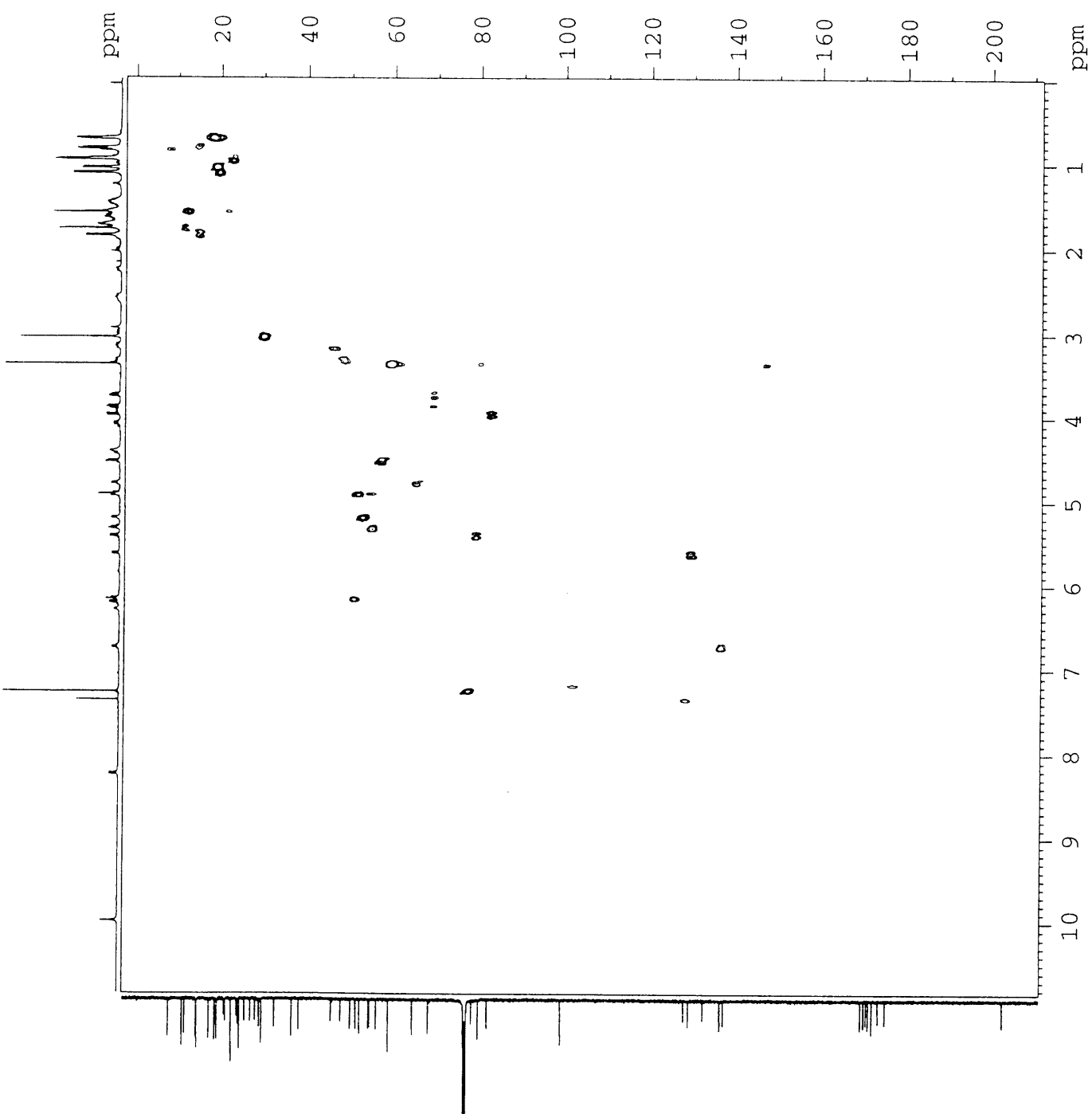
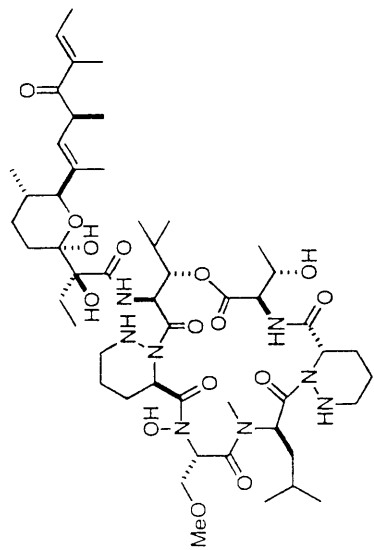










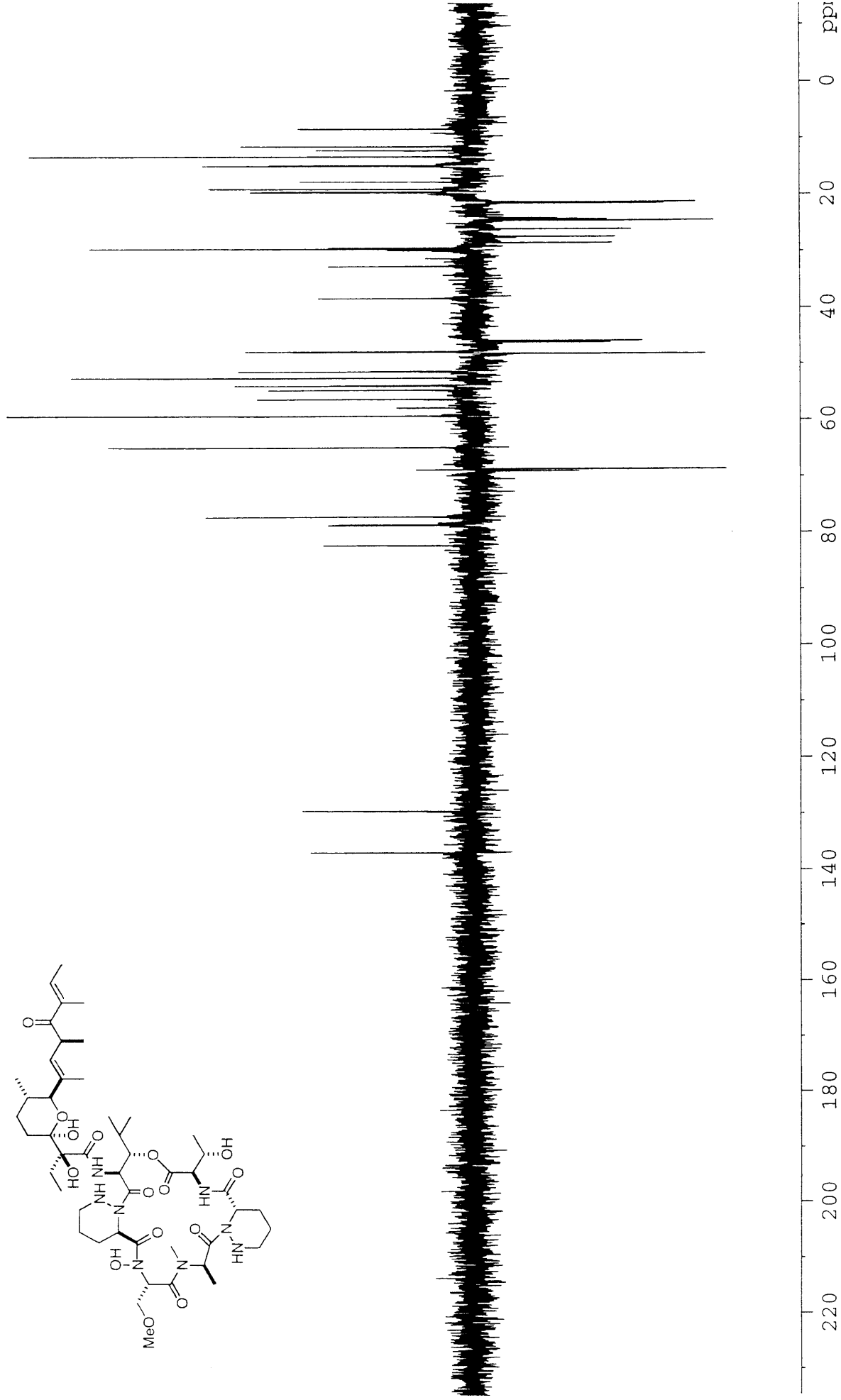
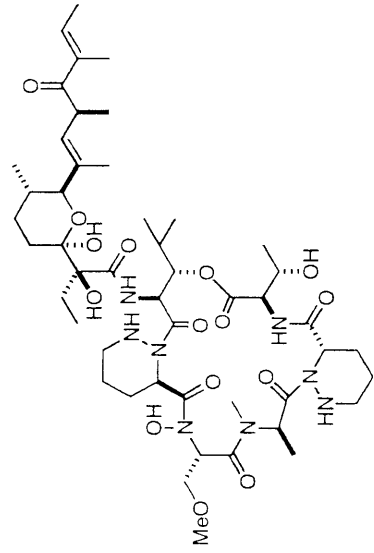






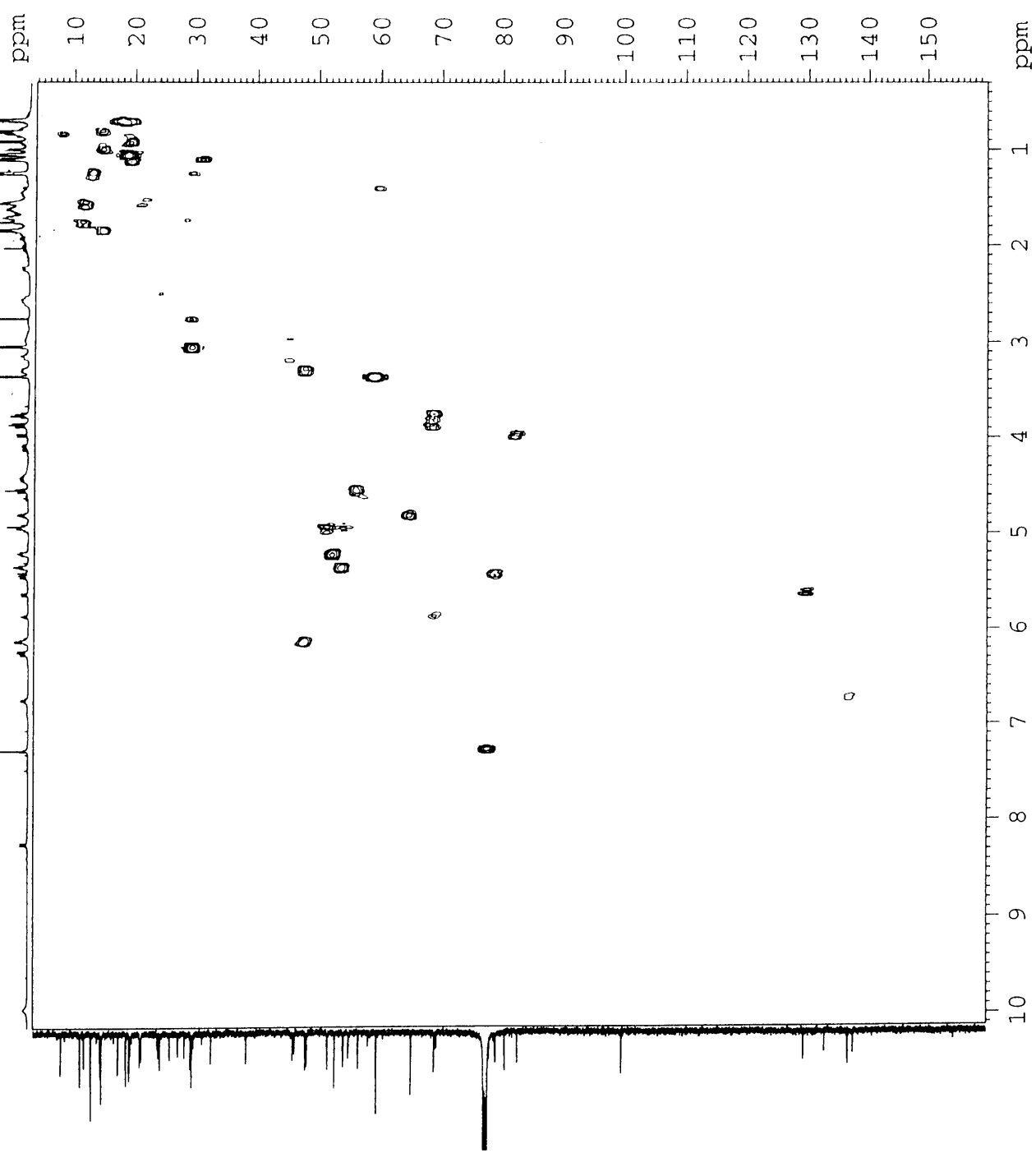


IV-JG-36  
DEPT  
CDCl<sub>3</sub>



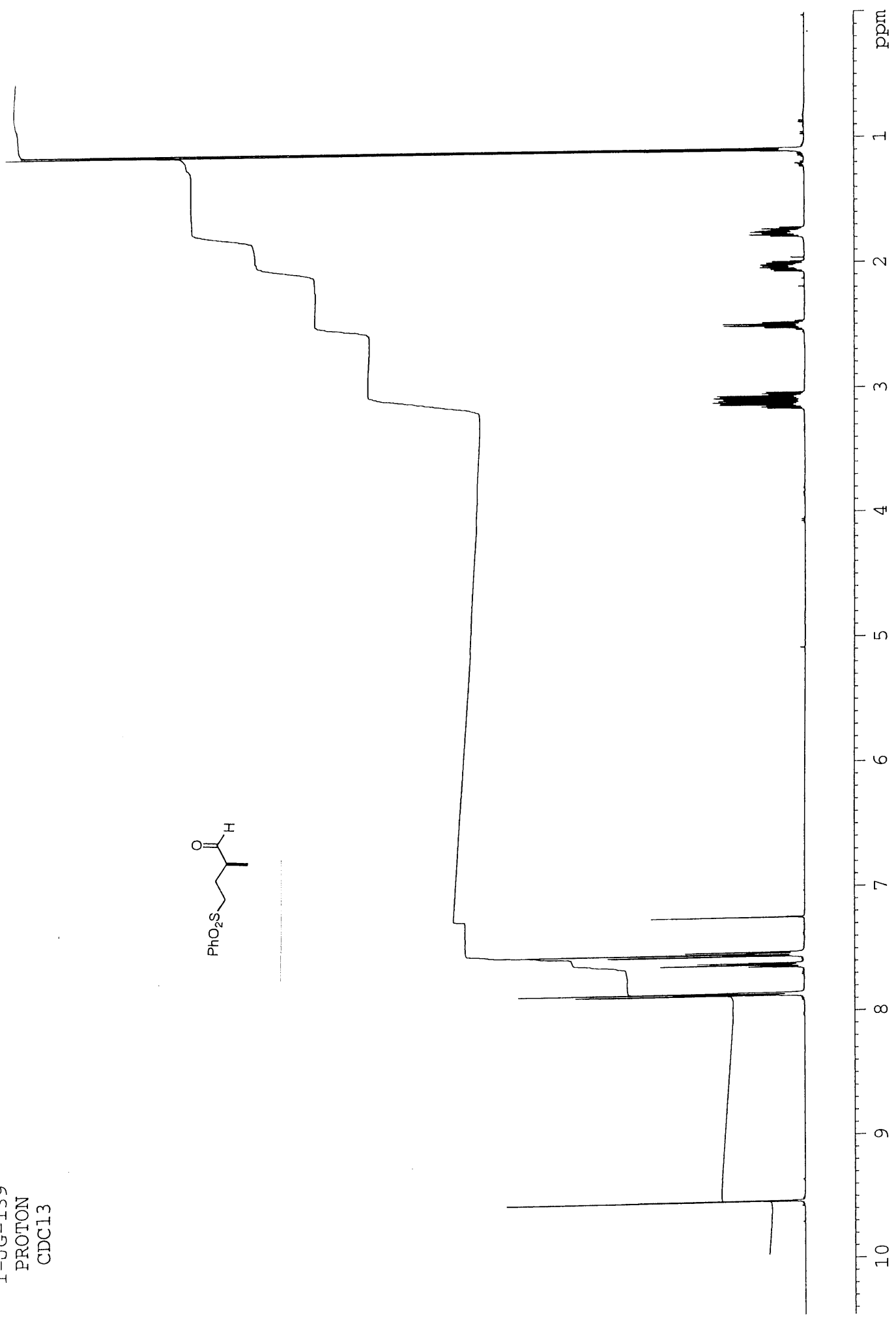
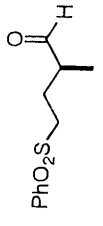


CDC13

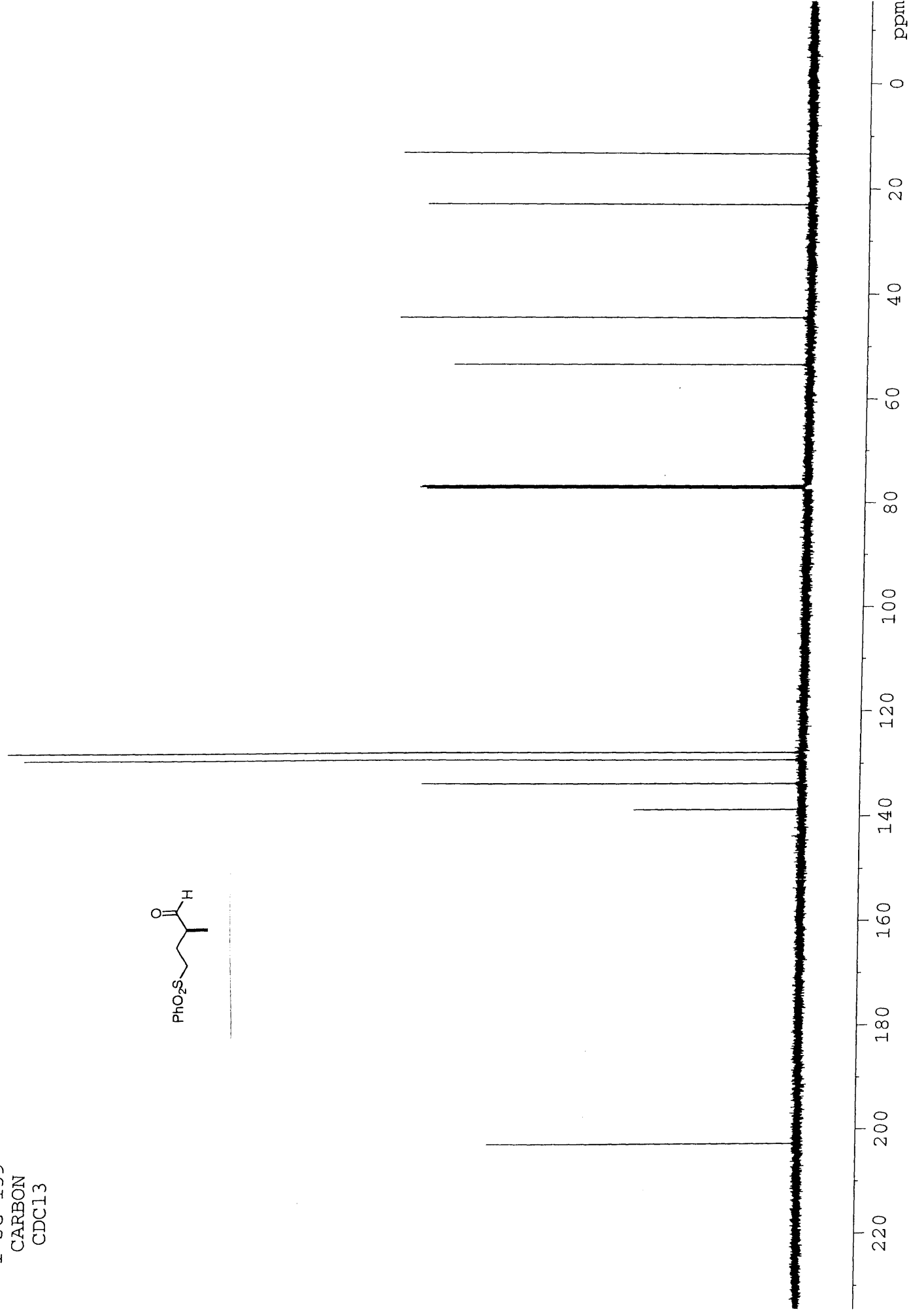
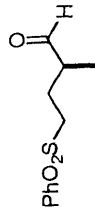




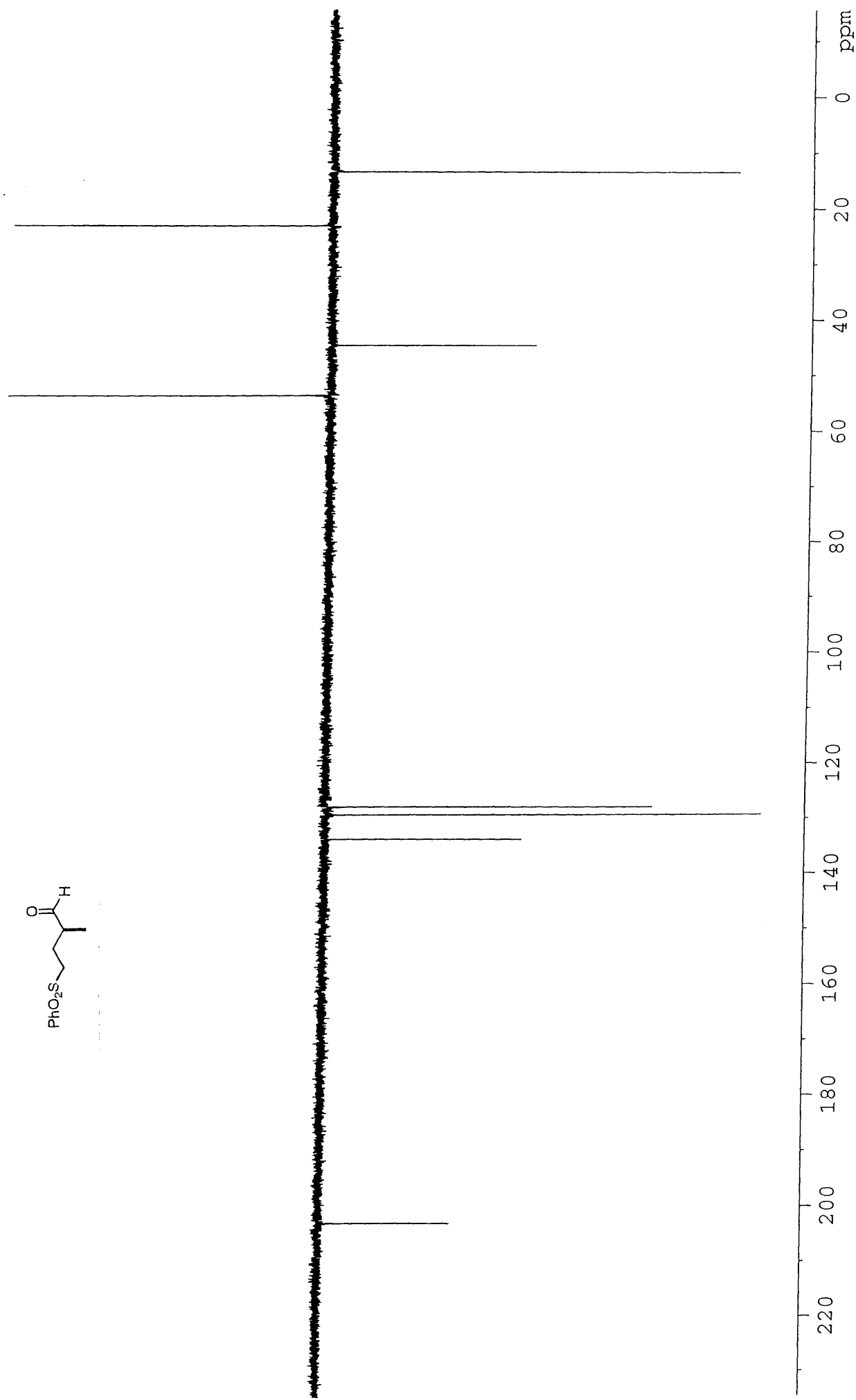
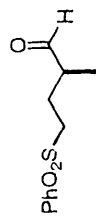
I-JG-139  
PROTON  
CDCl3



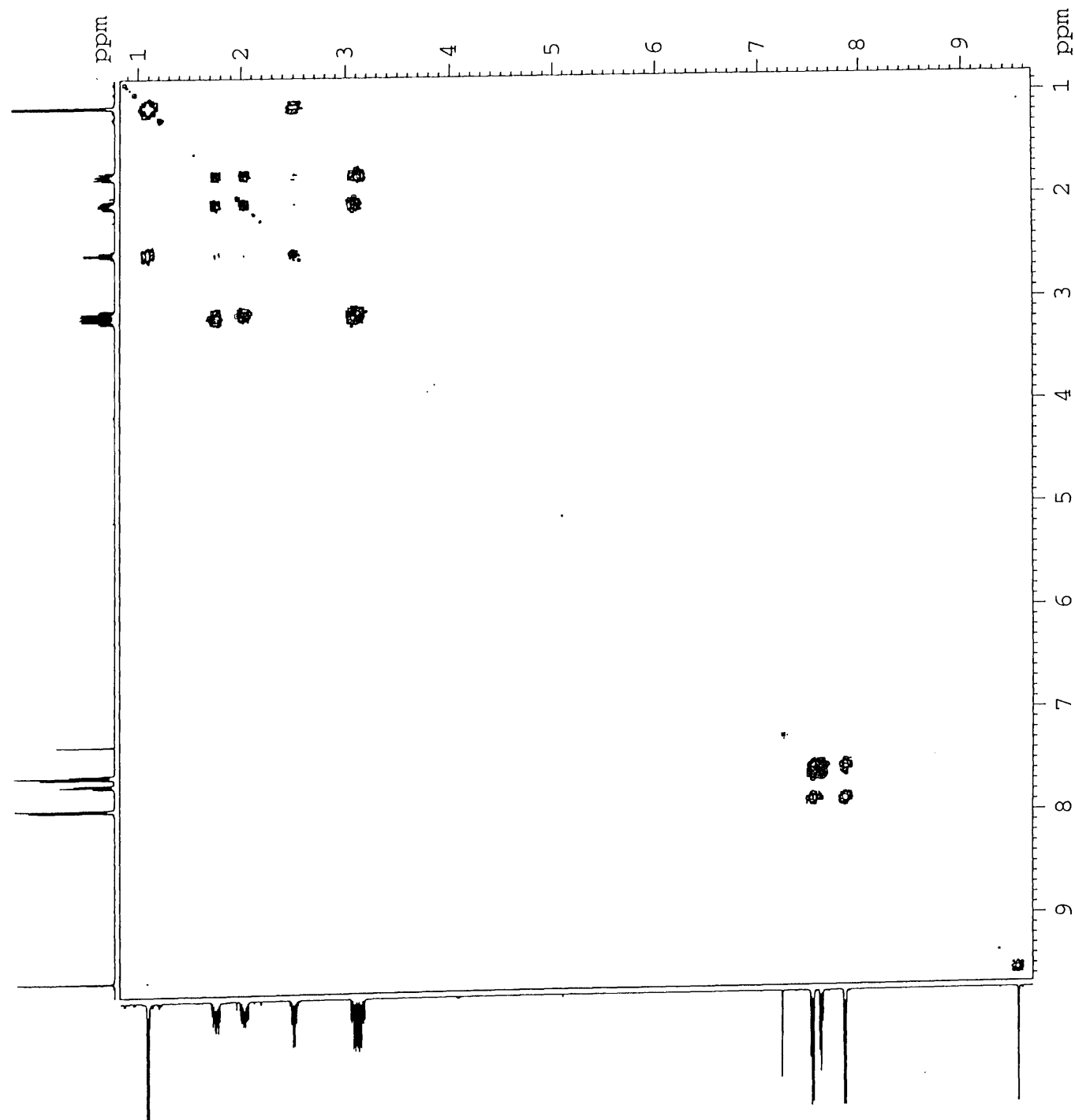
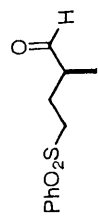
I-JG-139  
CARBON  
CDCl<sub>3</sub>



I-JG-139  
DEPT  
CDC13

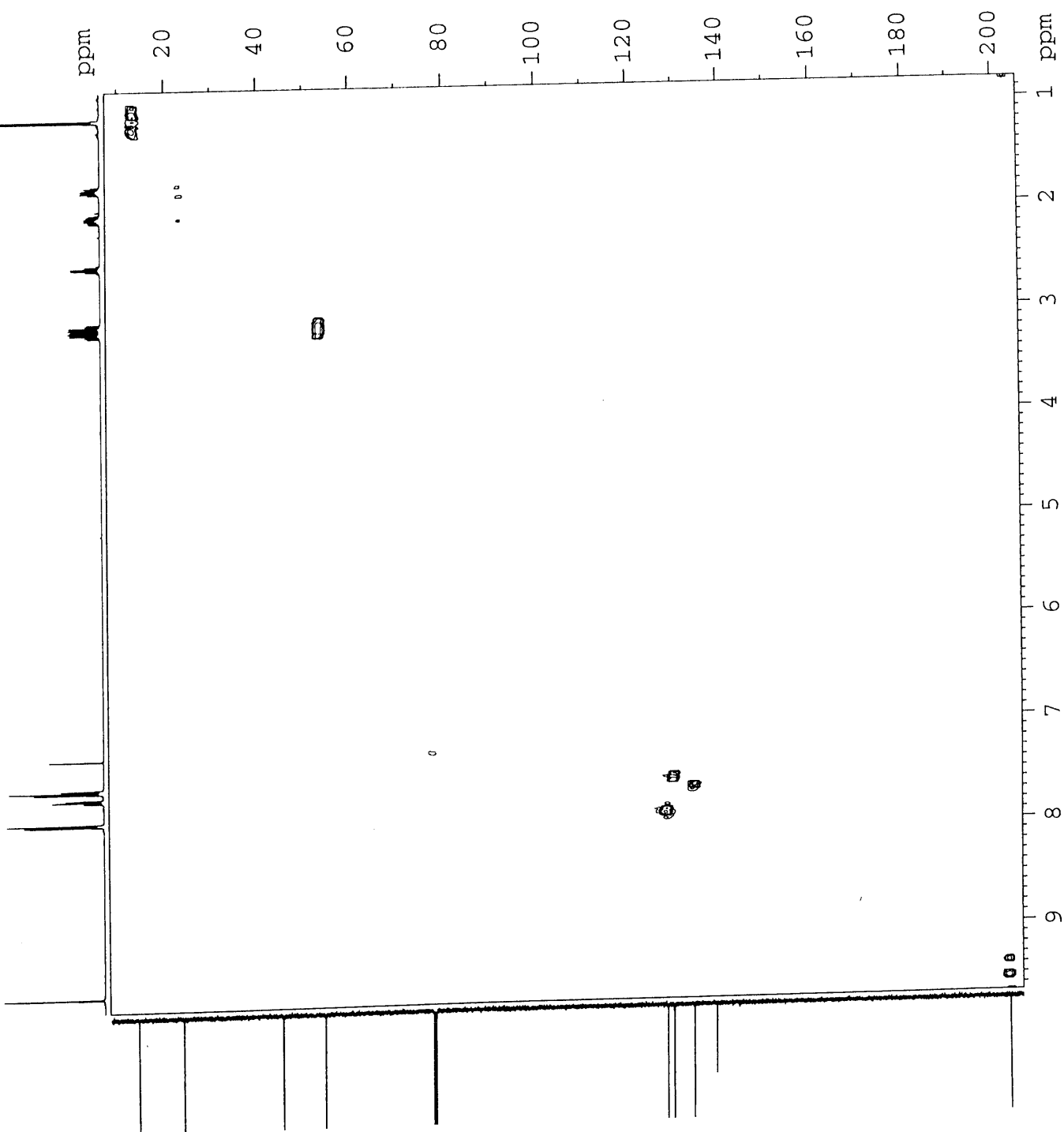
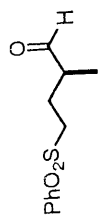


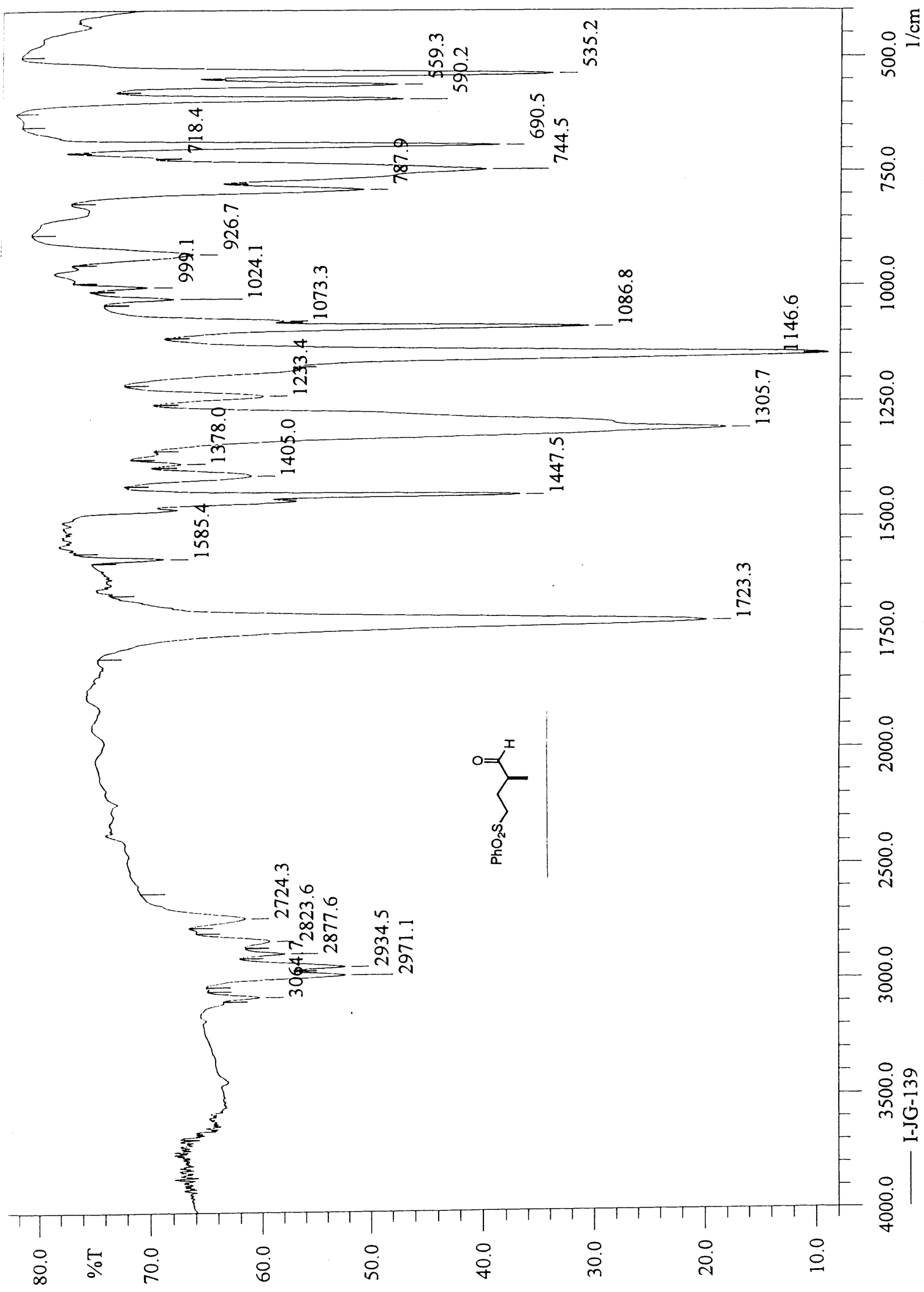
I-JG-139  
COSY  
CDC13





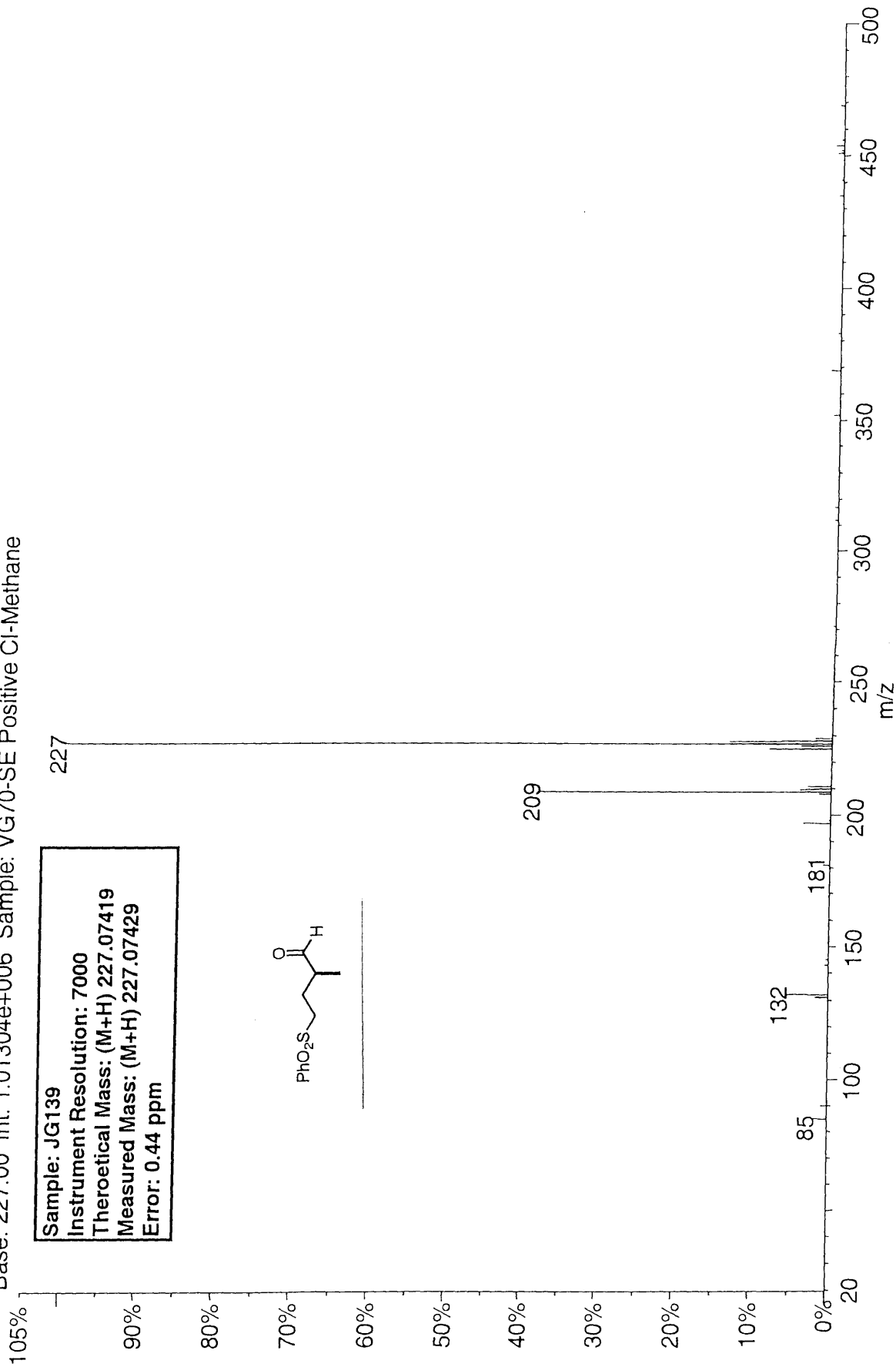
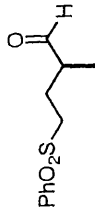
I-JG-139  
HMQC  
CDCl<sub>3</sub>



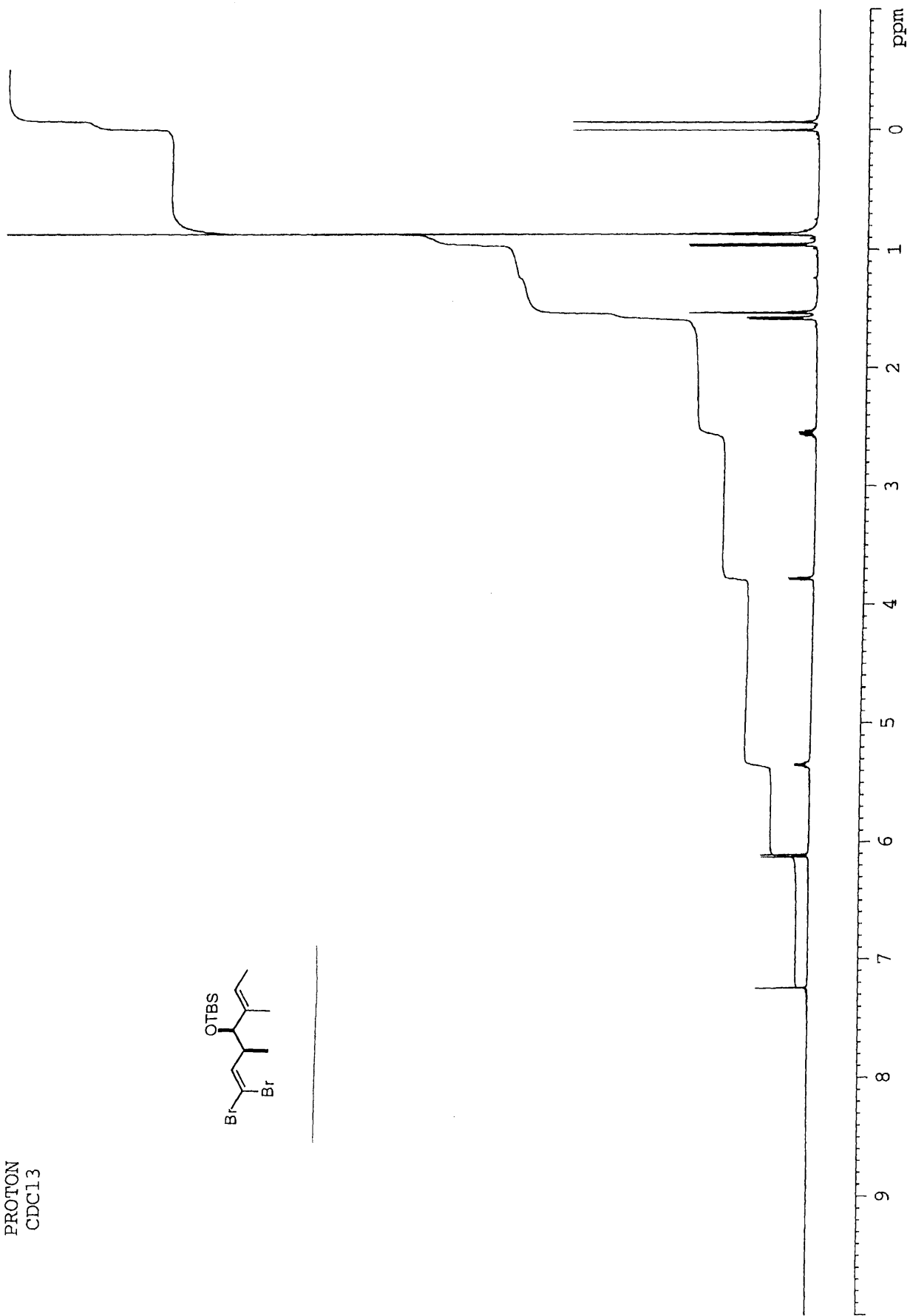
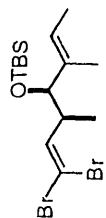


01260406: Scan 30 (6.80 min) - Back  
Base: 227.00 Int: 1.01304e+006 Sample: VG70-SE Positive CI-Methane

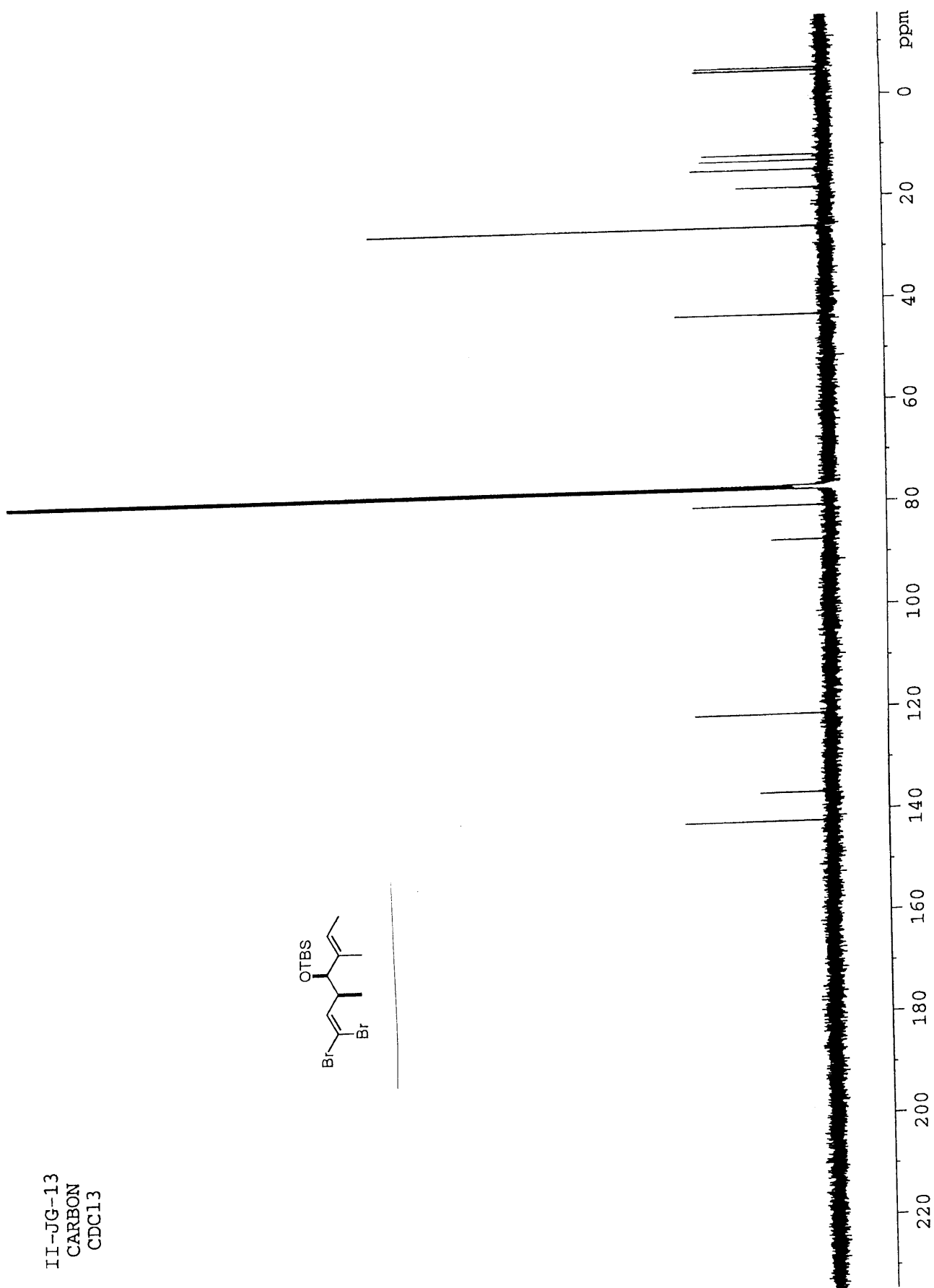
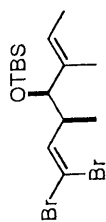
Sample: JG139  
Instrument Resolution: 7000  
Theoretical Mass: (M+H) 227.07419  
Measured Mass: (M+H) 227.07429  
Error: 0.44 ppm



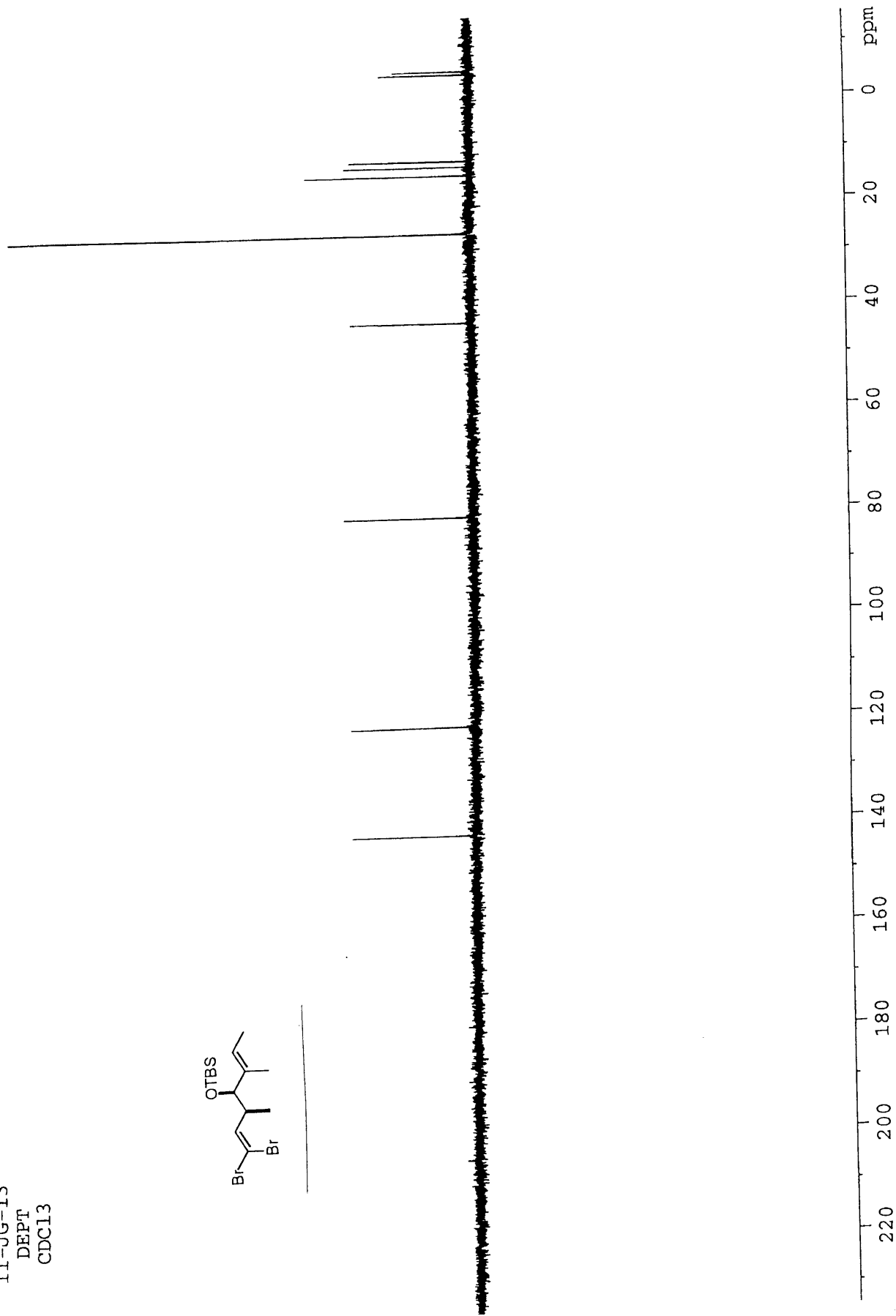
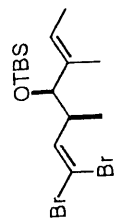
II-JG-13  
PROTON  
CDCl<sub>3</sub>



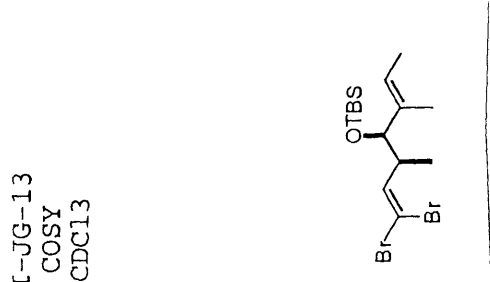
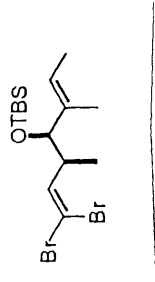
II-JG-13  
CARBON  
CDCl<sub>3</sub>



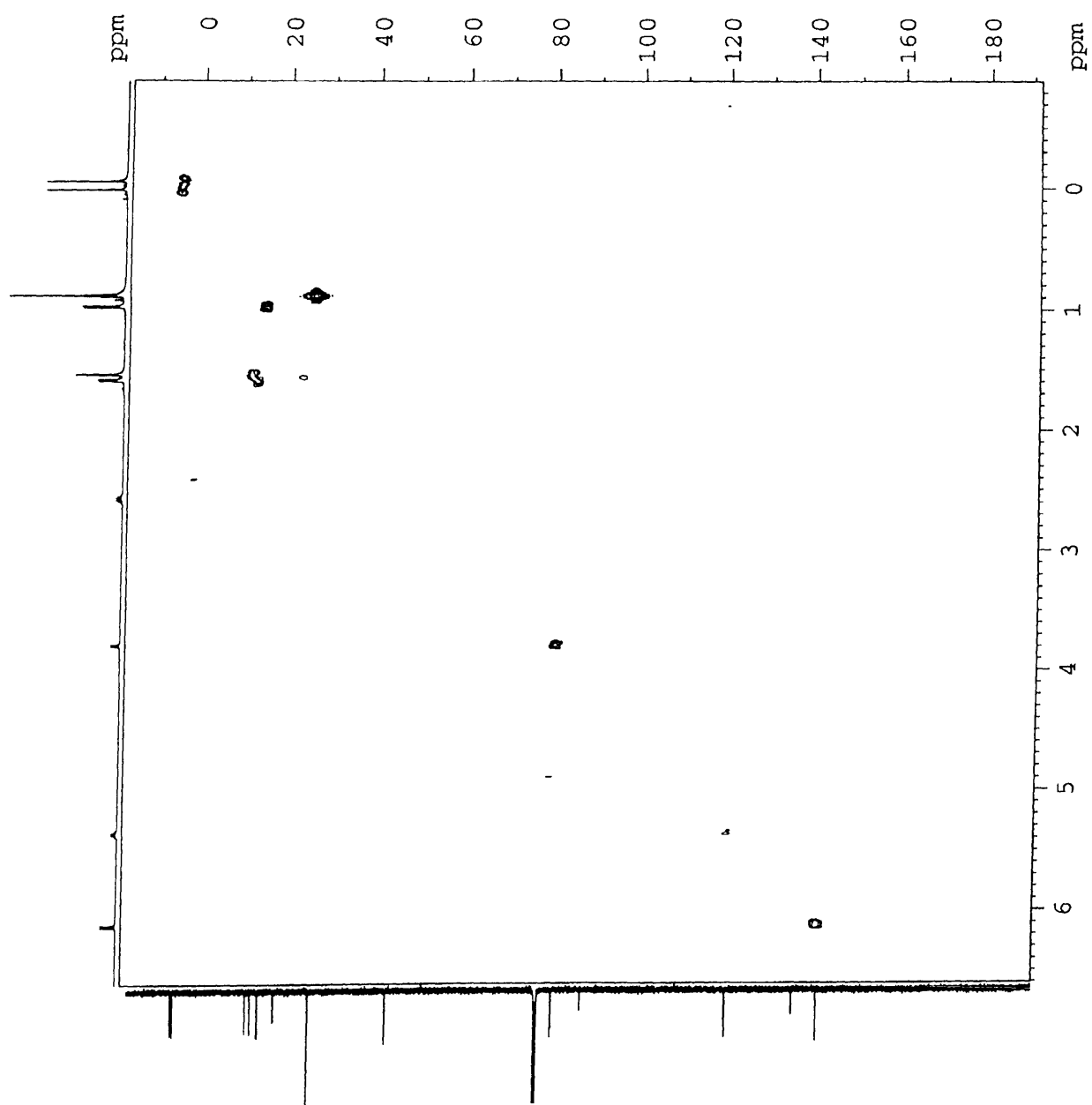
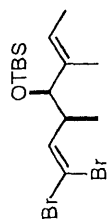
II-JG-13  
DEPT  
CDCl<sub>3</sub>



<sup>1</sup>H  
 COSY  
 CDCl<sub>3</sub>

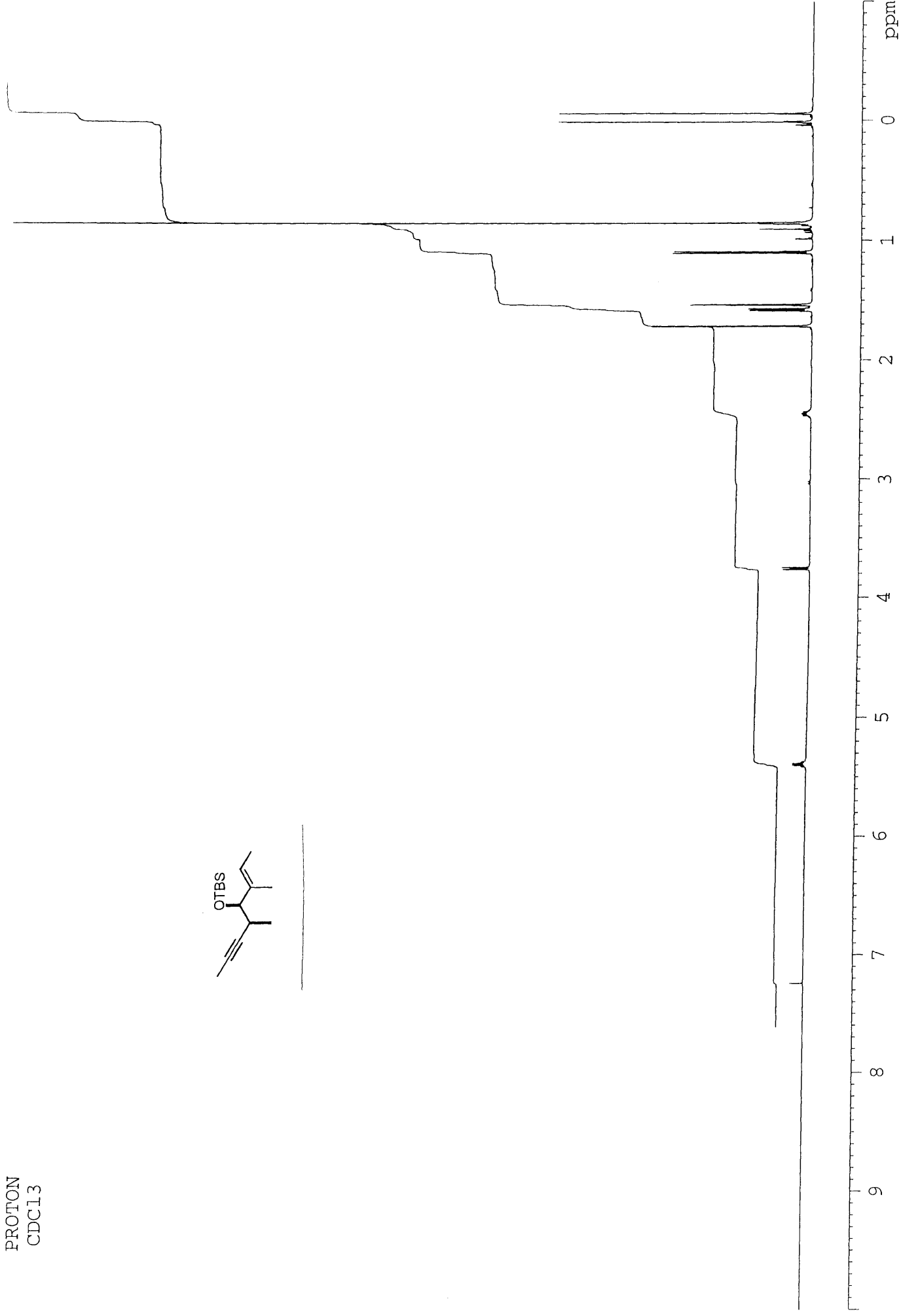
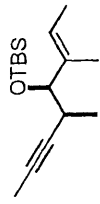


II-JG-13  
HMQC  
CDCl<sub>3</sub>

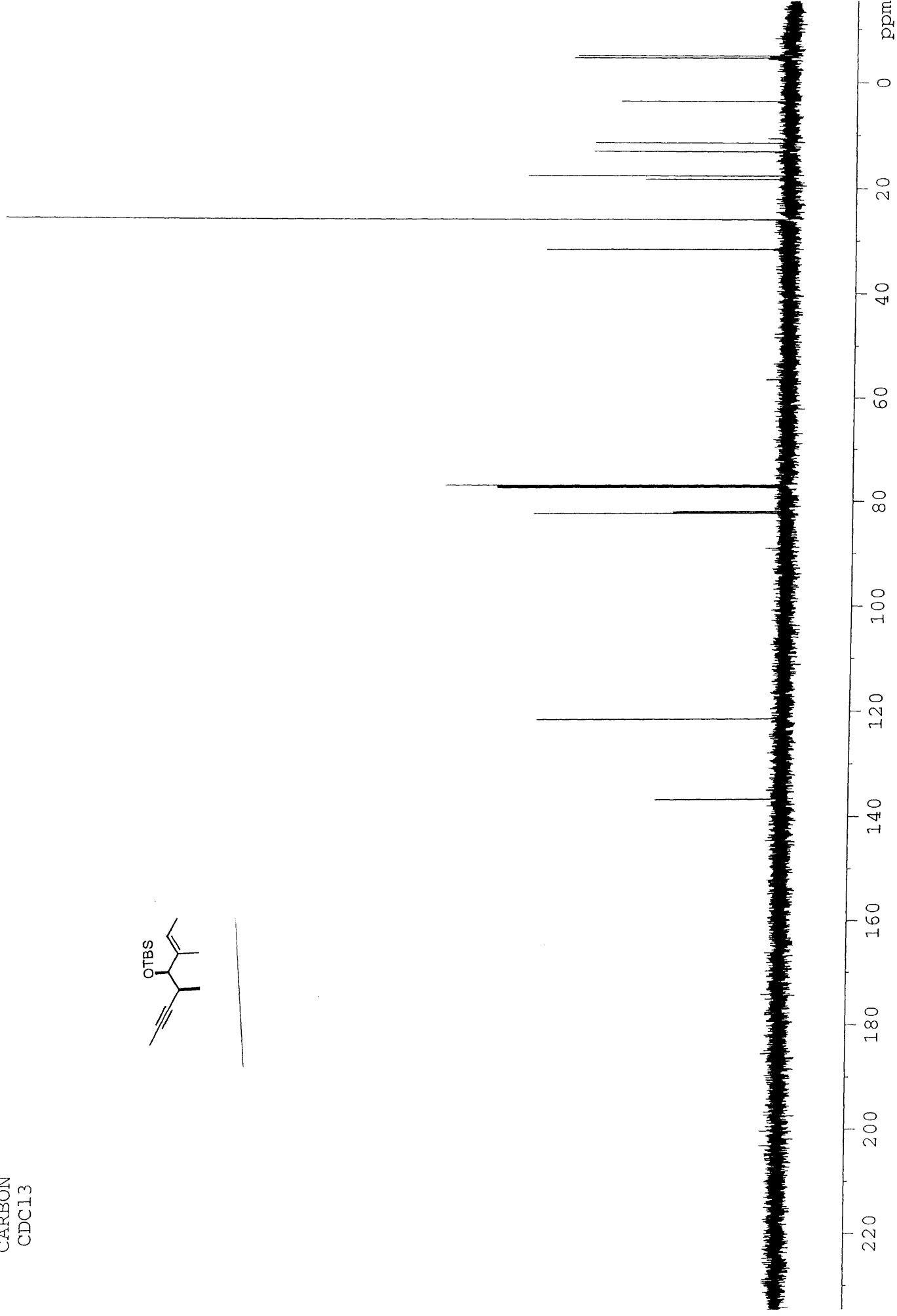
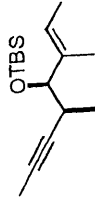




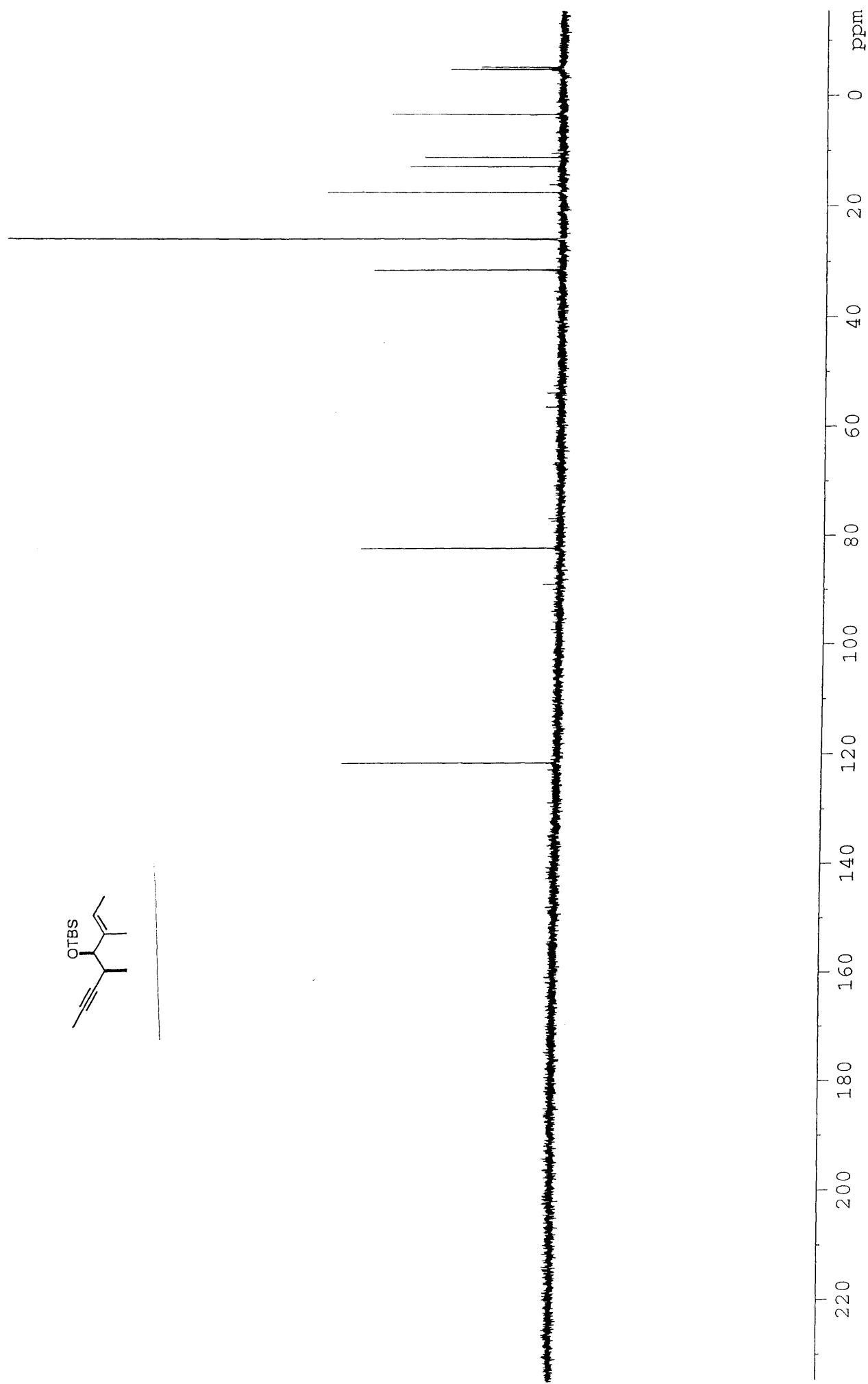
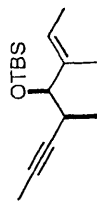
II-JG-24  
PROTON  
CDCl<sub>3</sub>



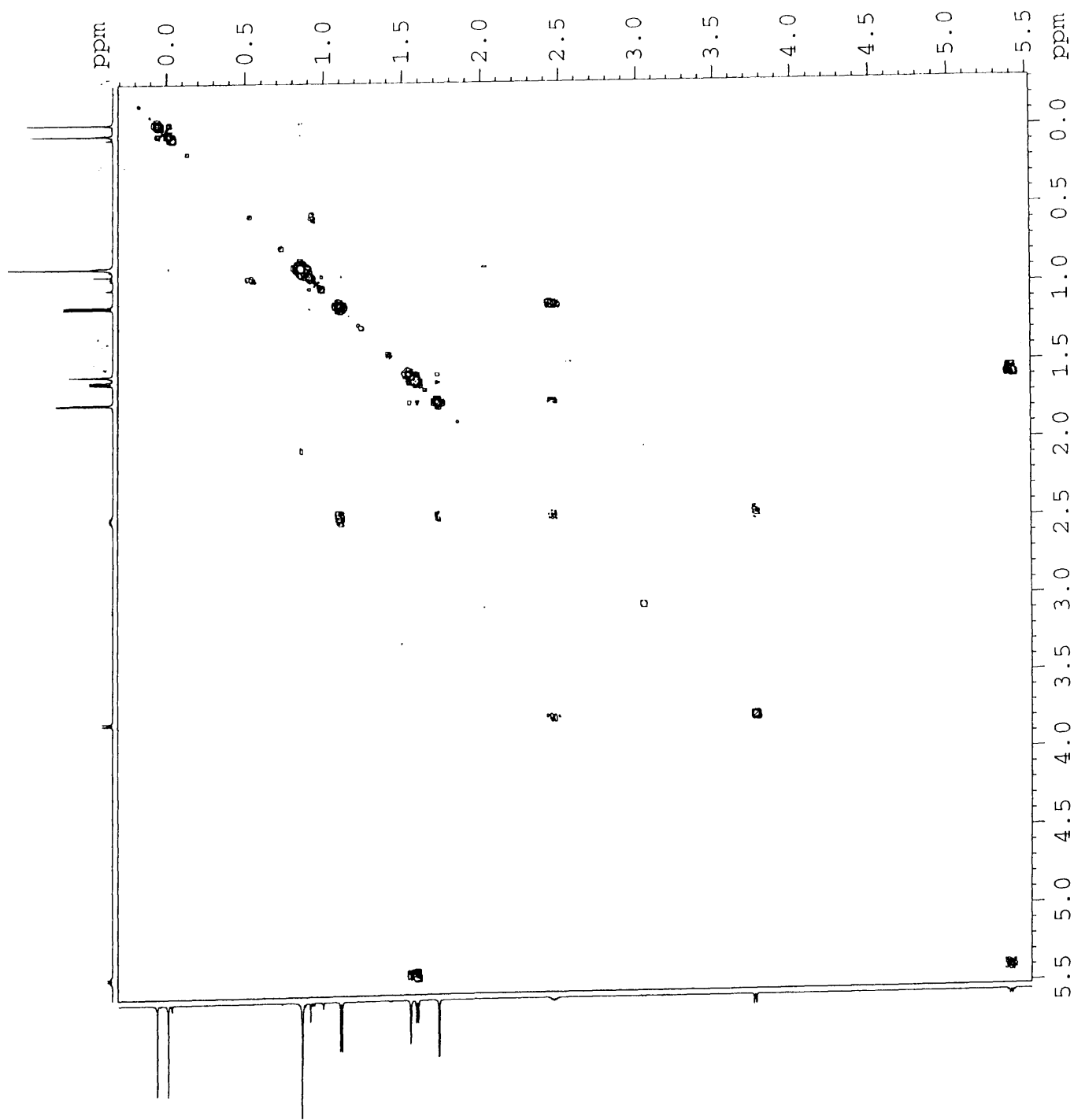
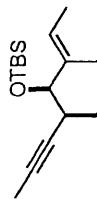
II-JG-24  
CARBON  
CDCl<sub>3</sub>

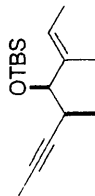
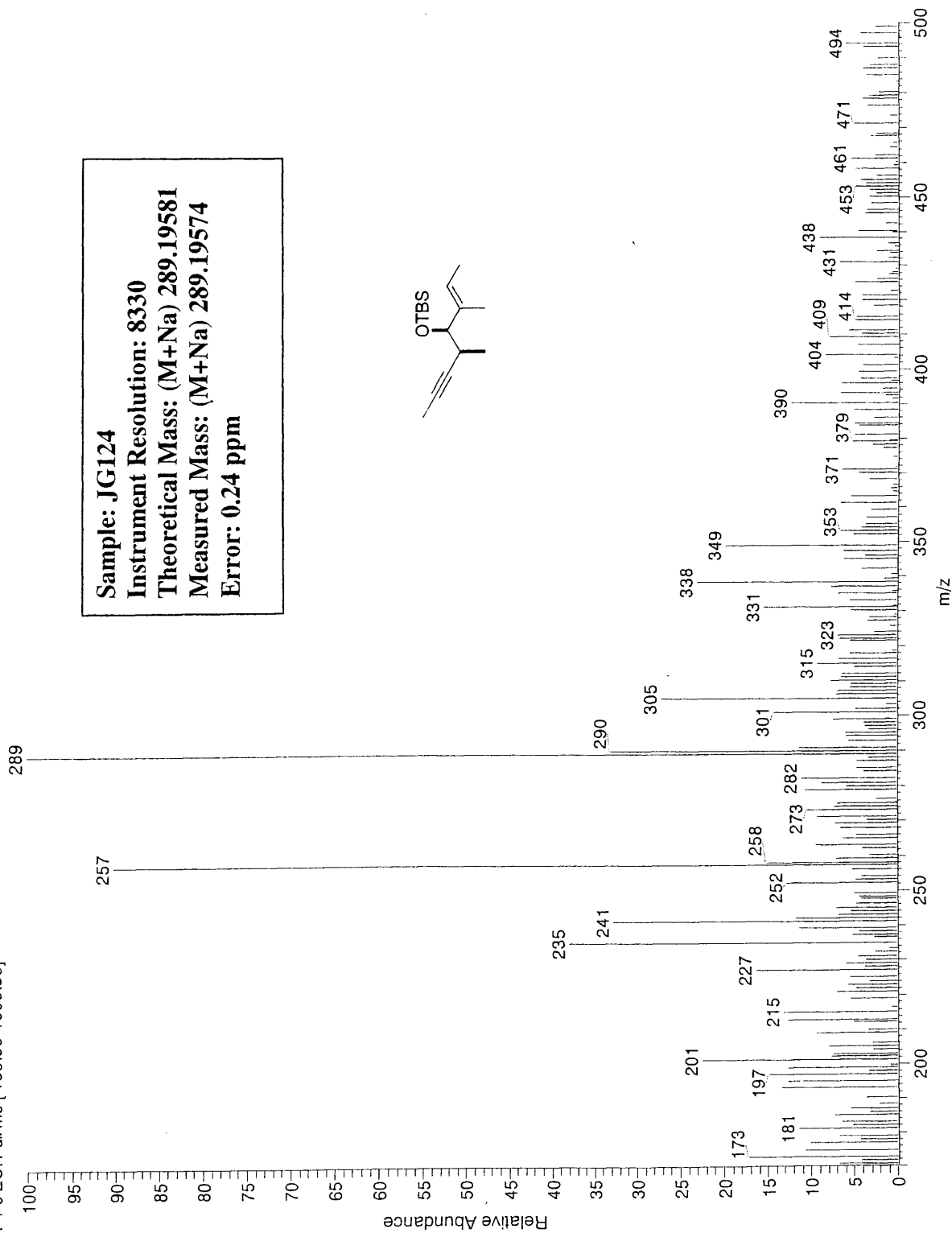


II-JG-24  
DEPT  
CDCl<sub>3</sub>



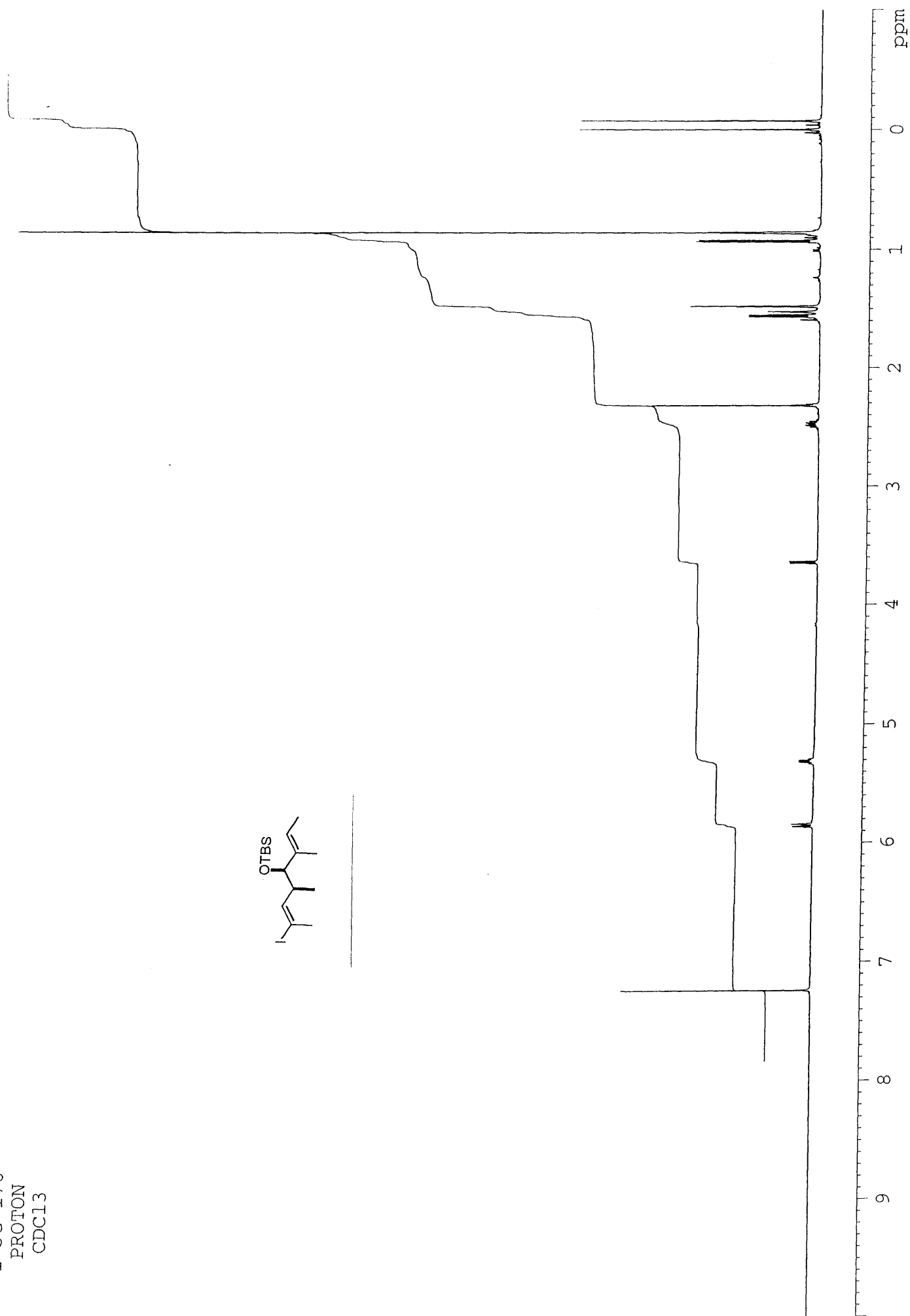
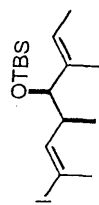
II-JG-24  
COSY  
CDC13



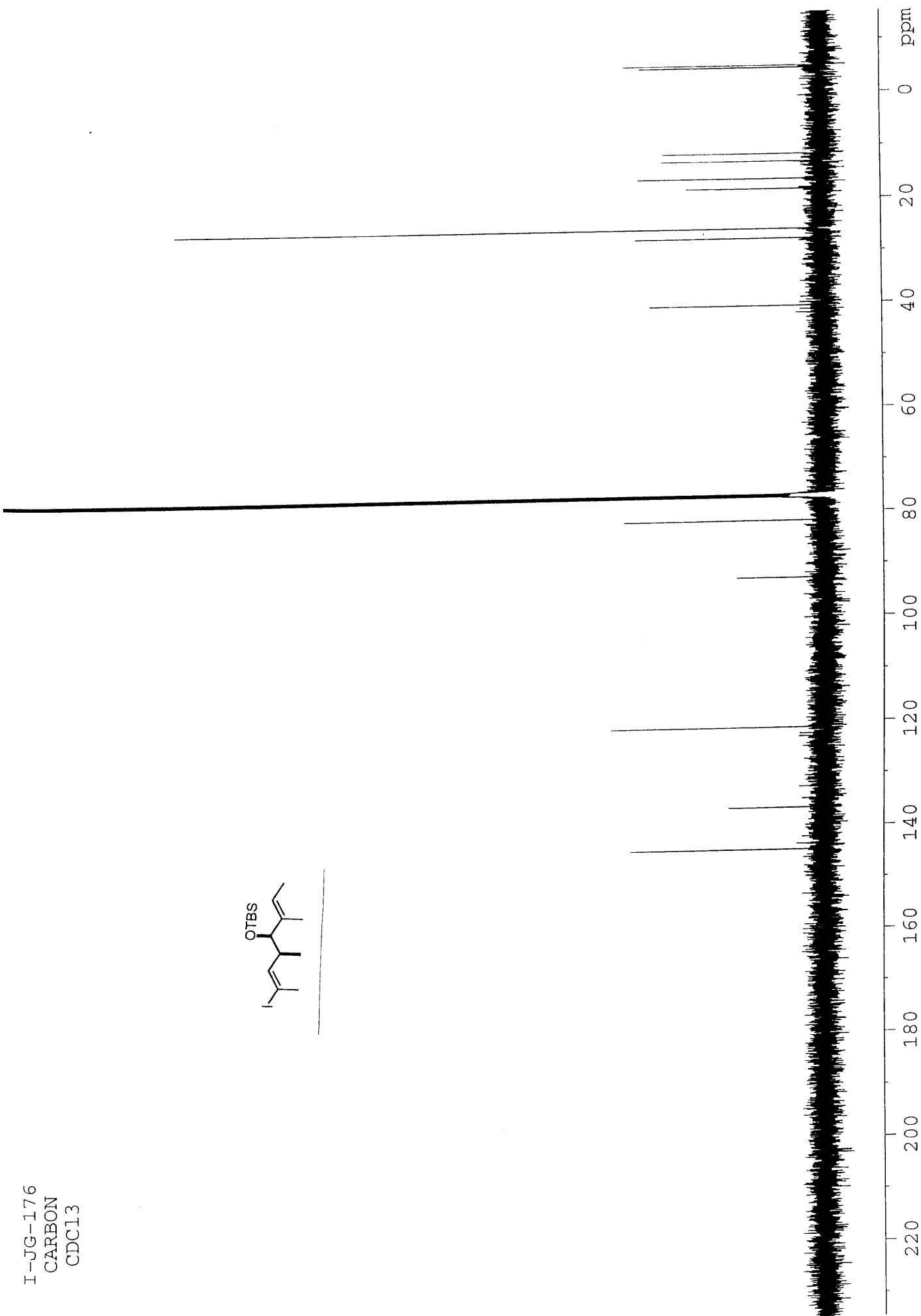
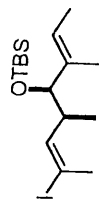


Sample: JG124  
Instrument Resolution: 8330  
Theoretical Mass: (M+Na) 289.19581  
Measured Mass: (M+Na) 289.19574  
Error: 0.24 ppm

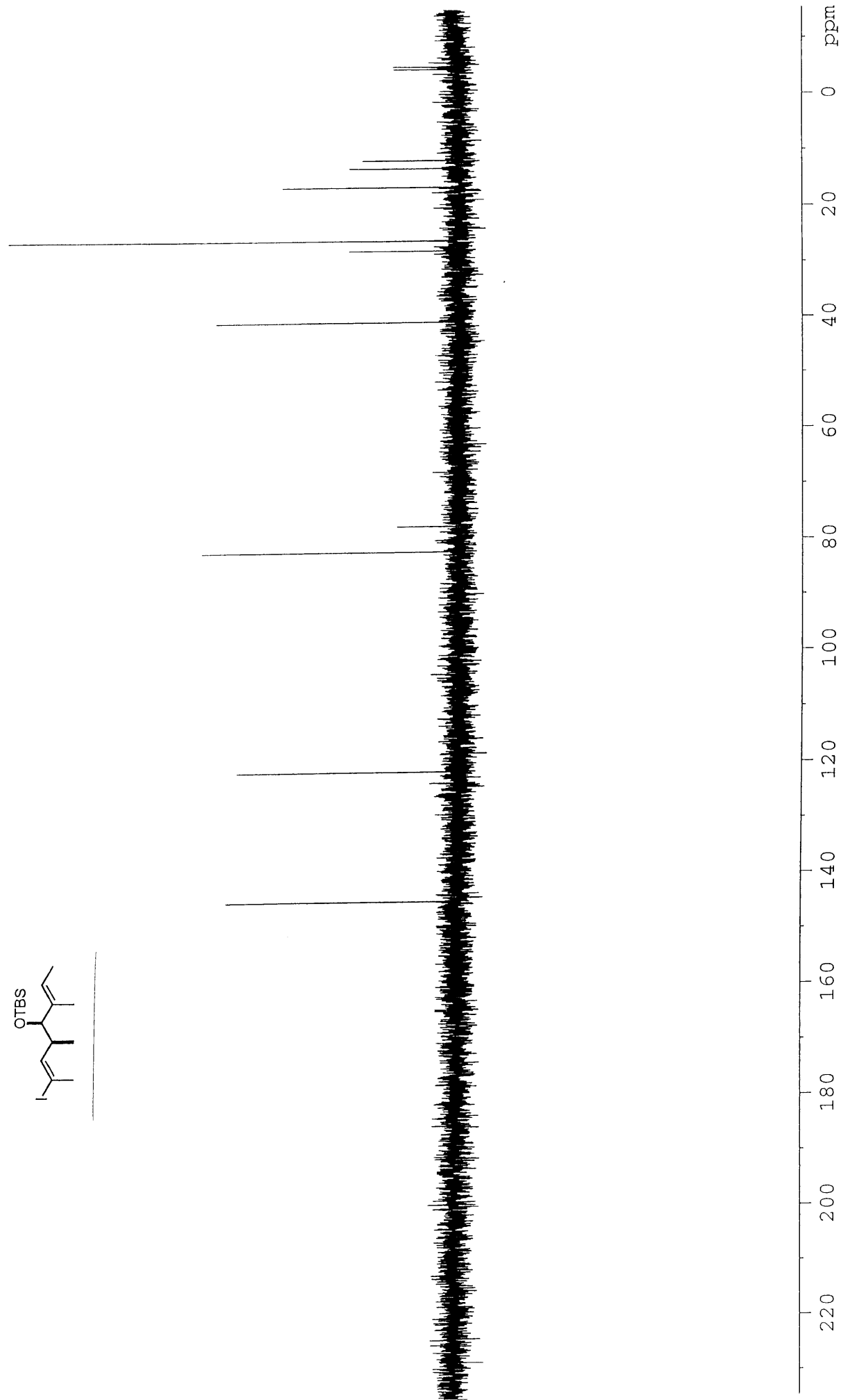
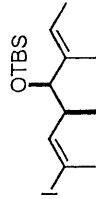
I-JG-176  
PROTON  
CDCl3



I-JG-176  
CARBON  
CDCl3

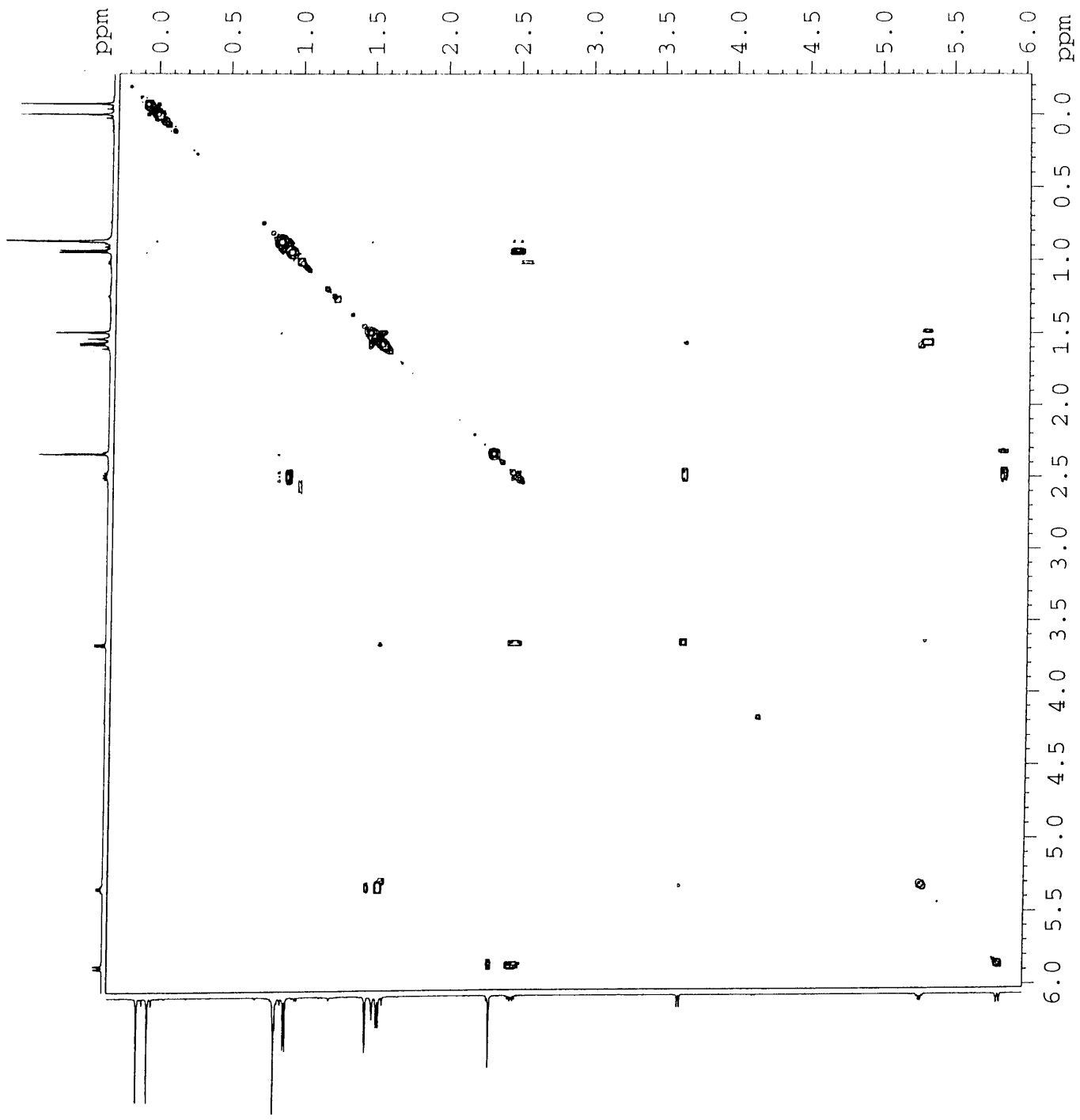


I-JG-176  
DEPT  
CDCl3

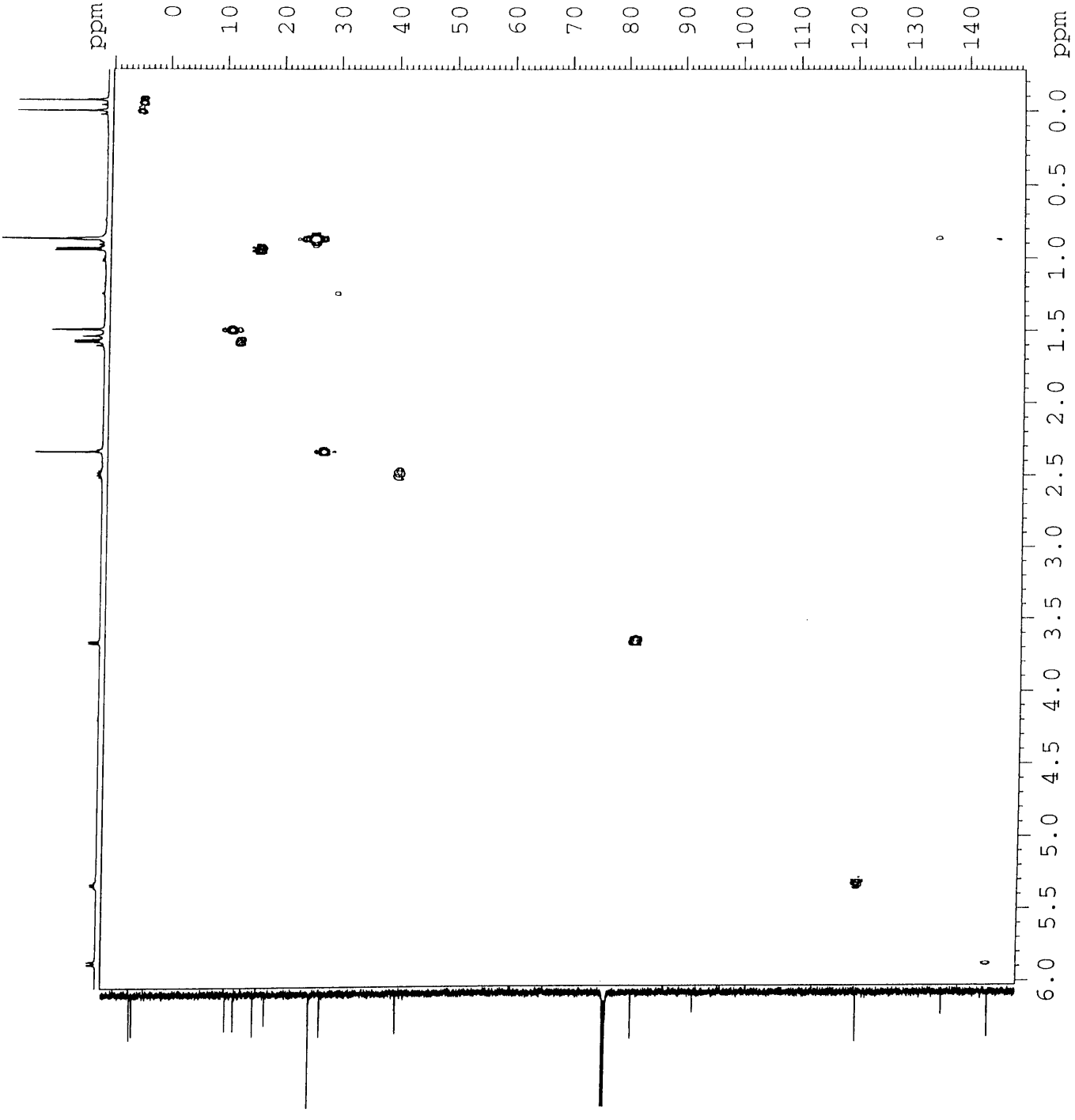
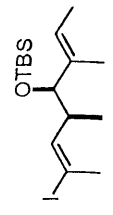


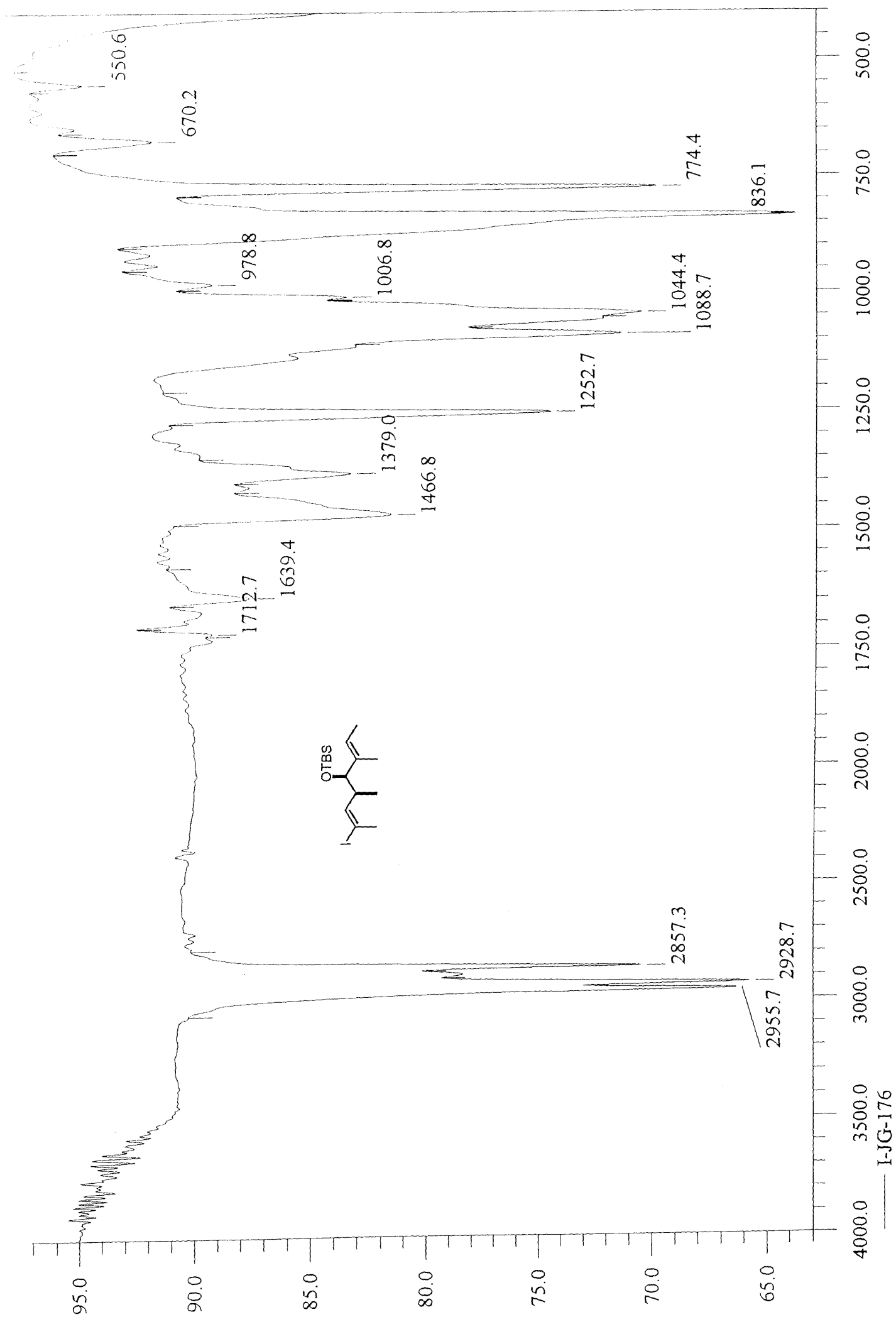


CDC13

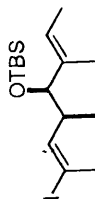
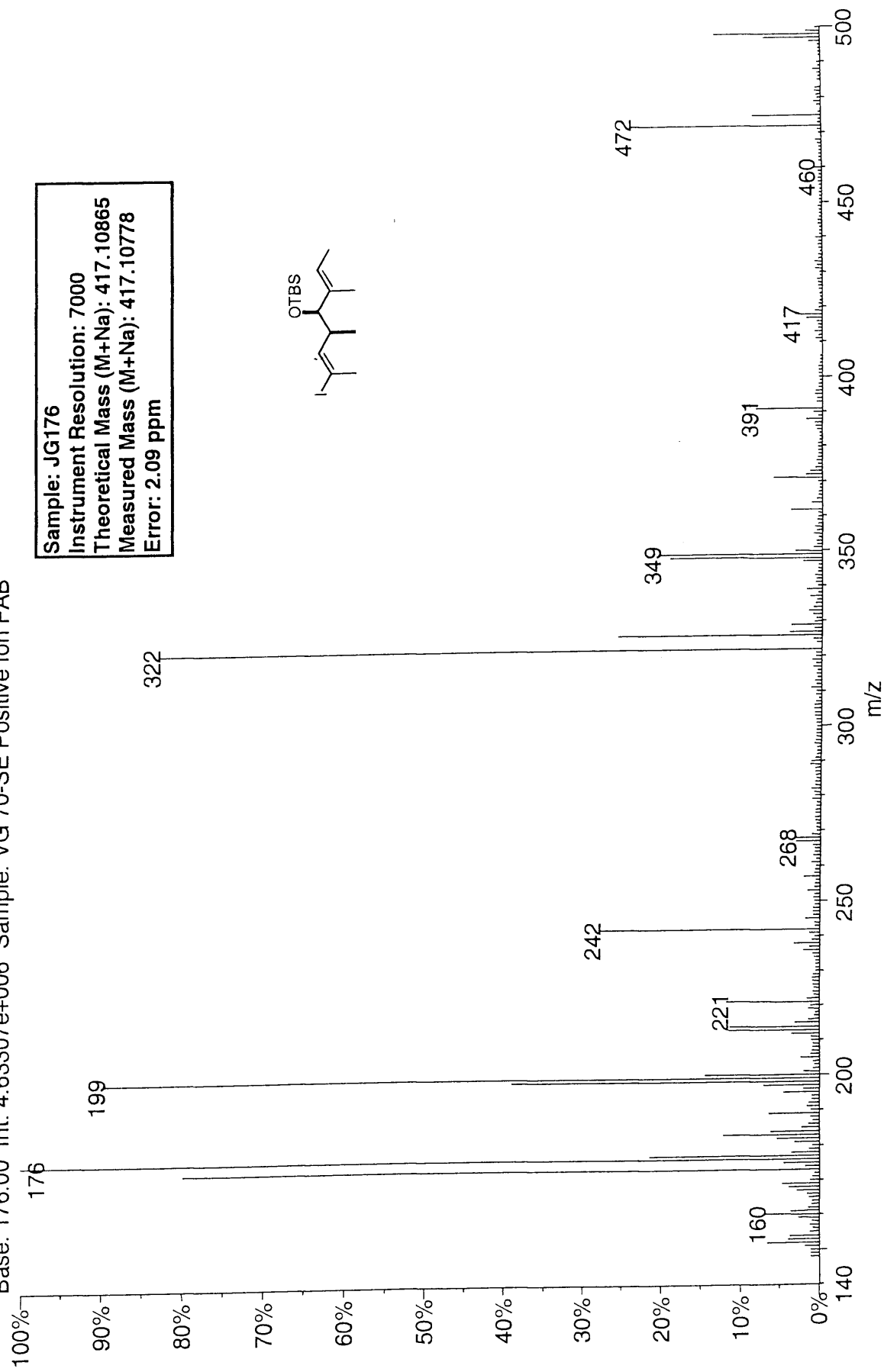


I-JG-176  
HMQC  
CDCl<sub>3</sub>

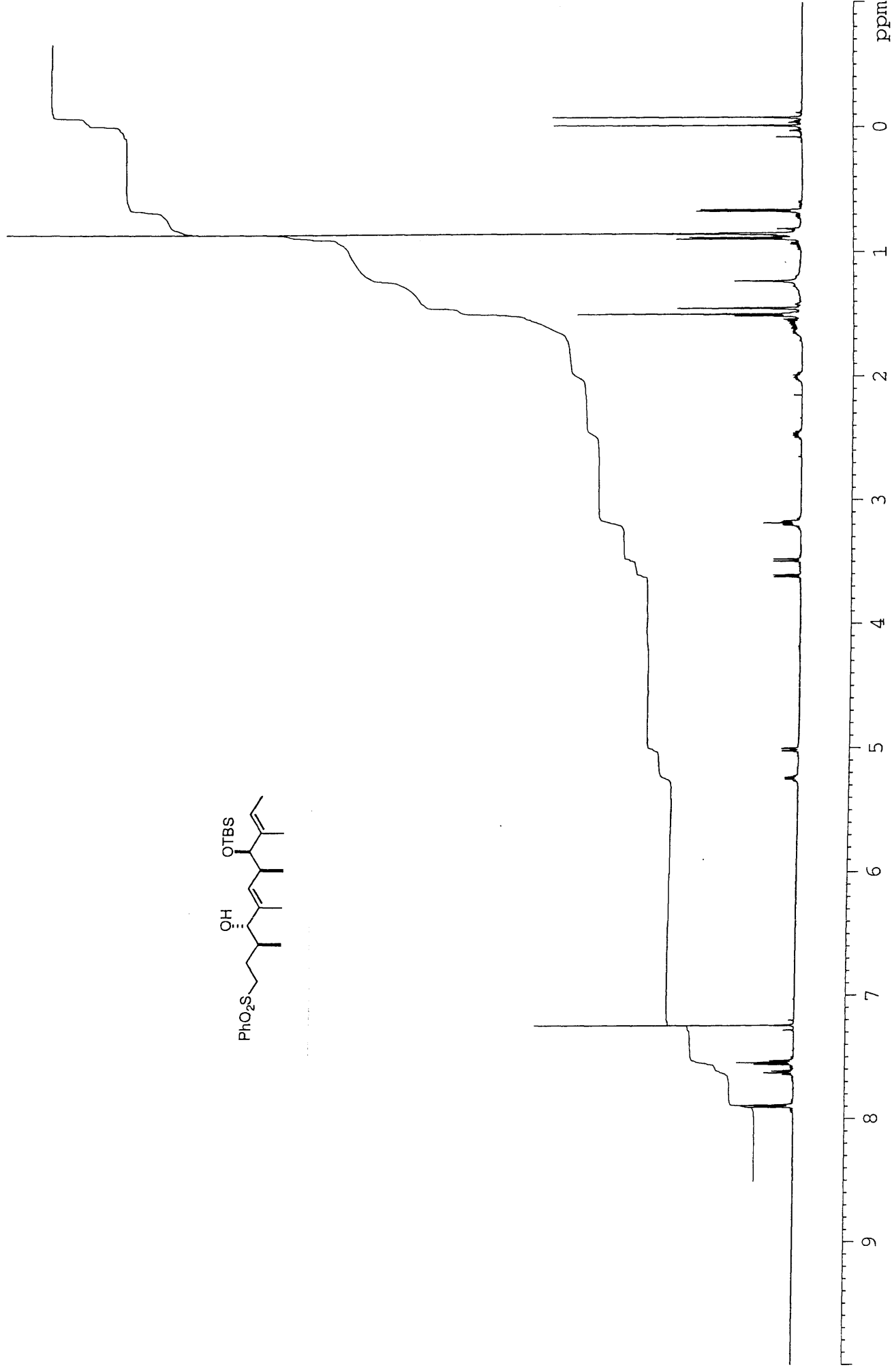
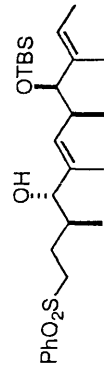




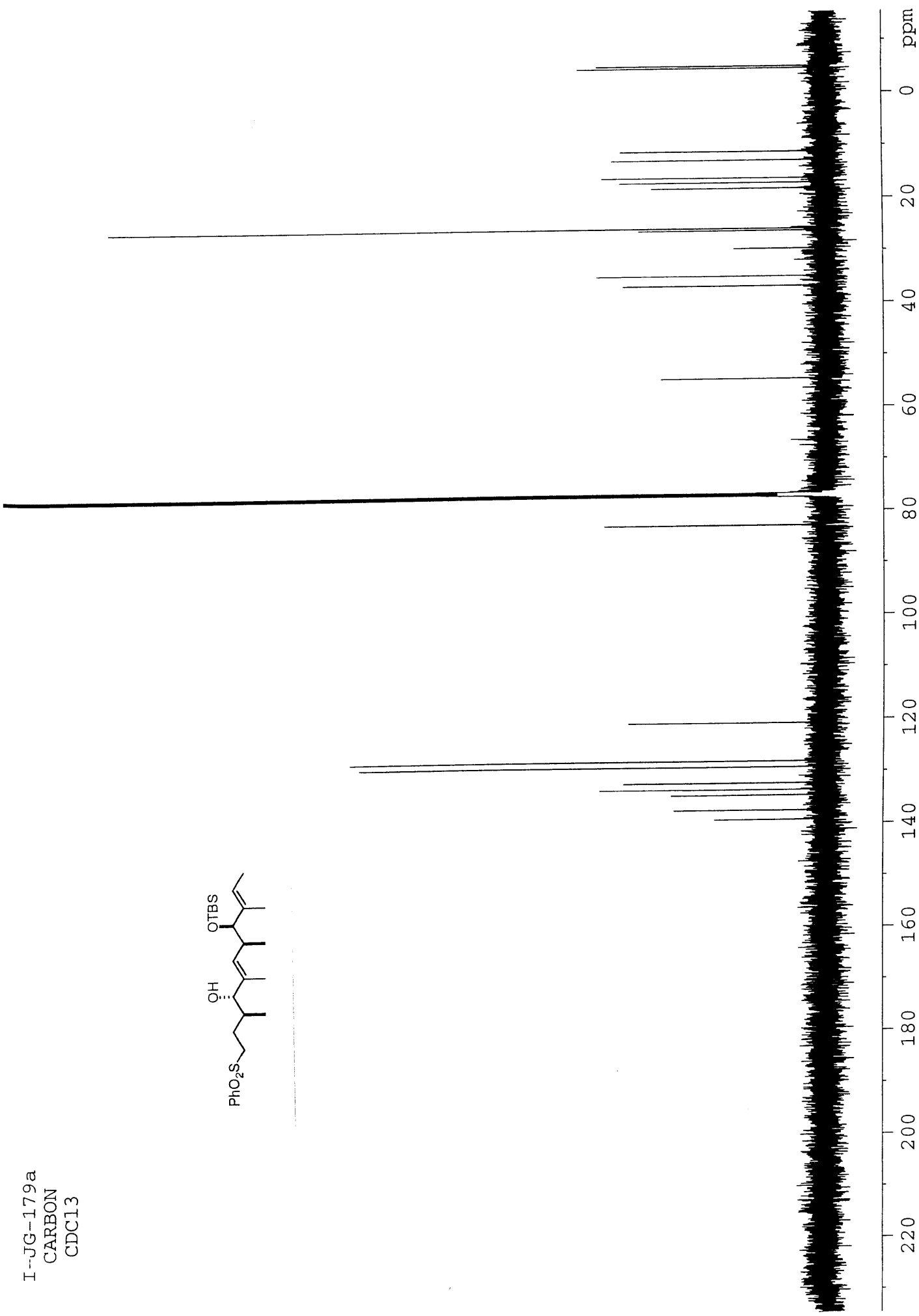
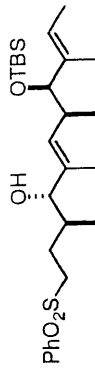
02020806: Scan 395 (78.90 min) - Back  
Base: 176.00 Int: 4.63307e+006 Sample: VG 70-SE Positive Ion FAB



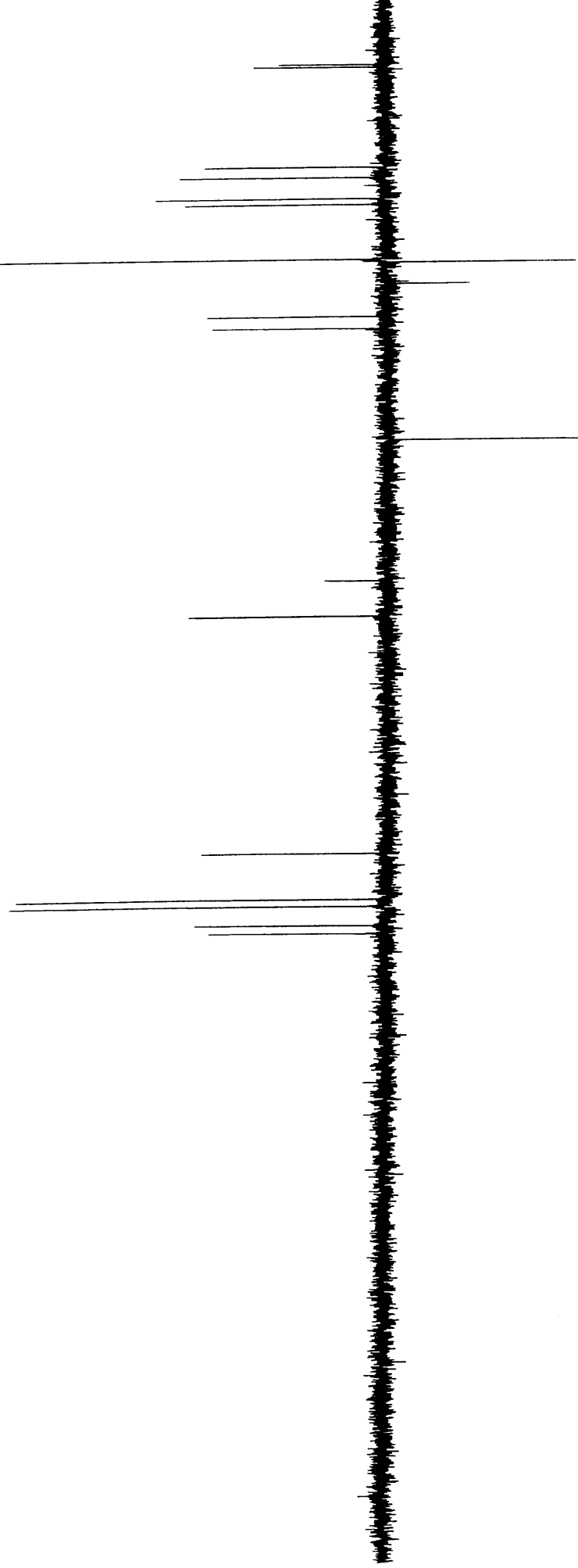
I-JG-179a  
PROTON  
CDCl3



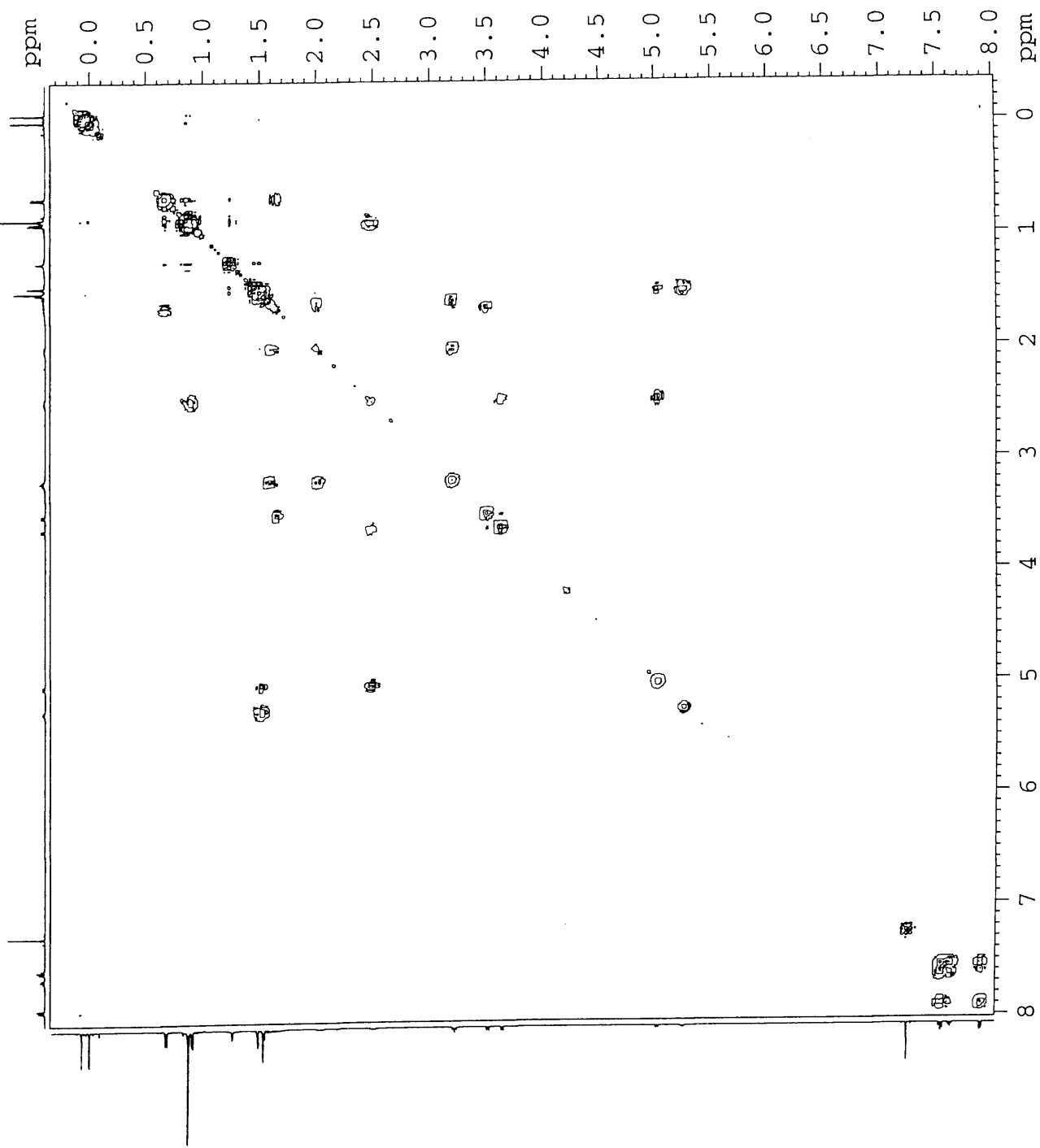
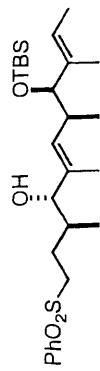
I--JG-179a  
CARBON  
CDC13



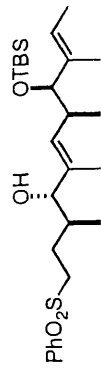
CDC13

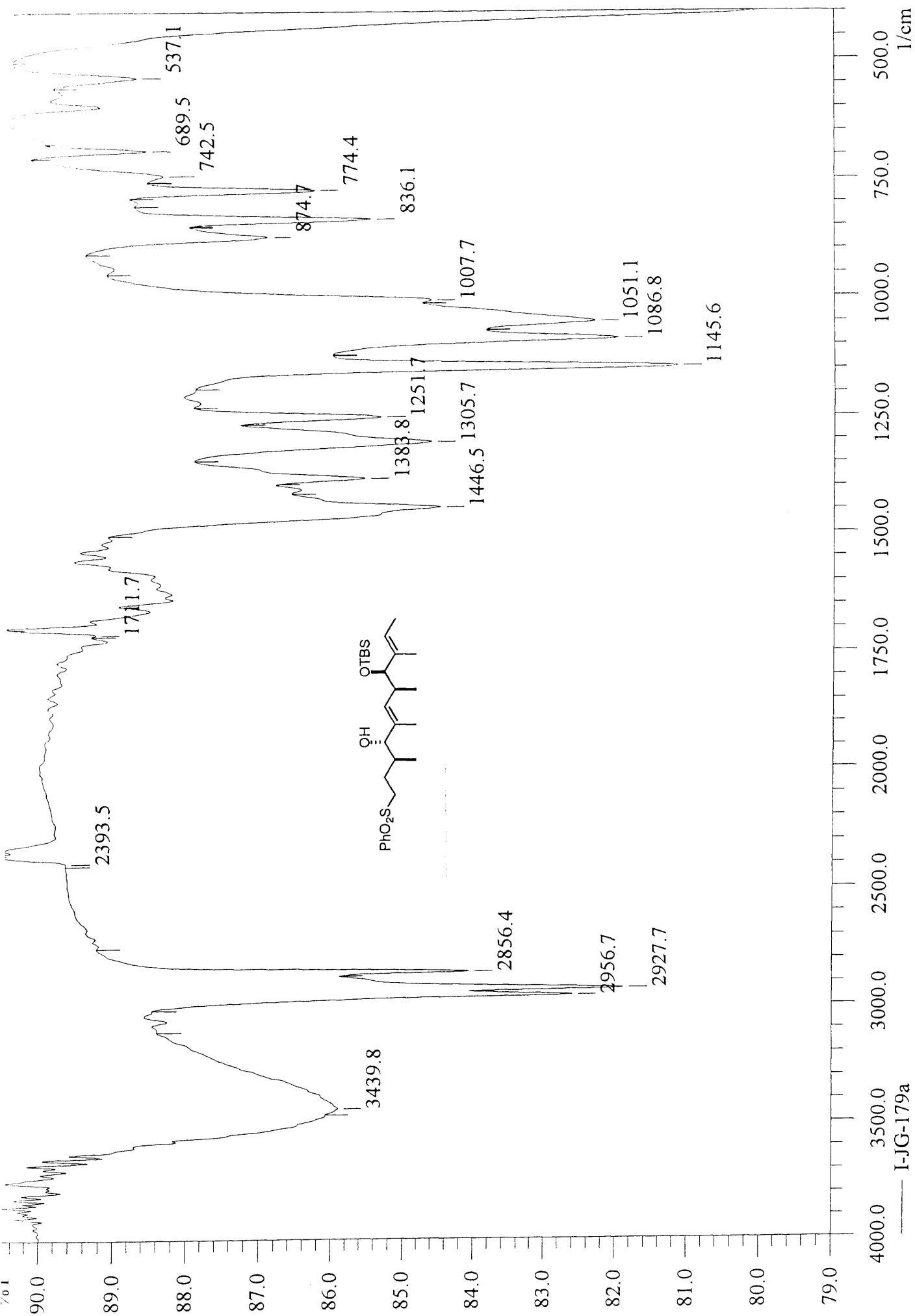


I--JG-179a  
COSY  
CDCl3

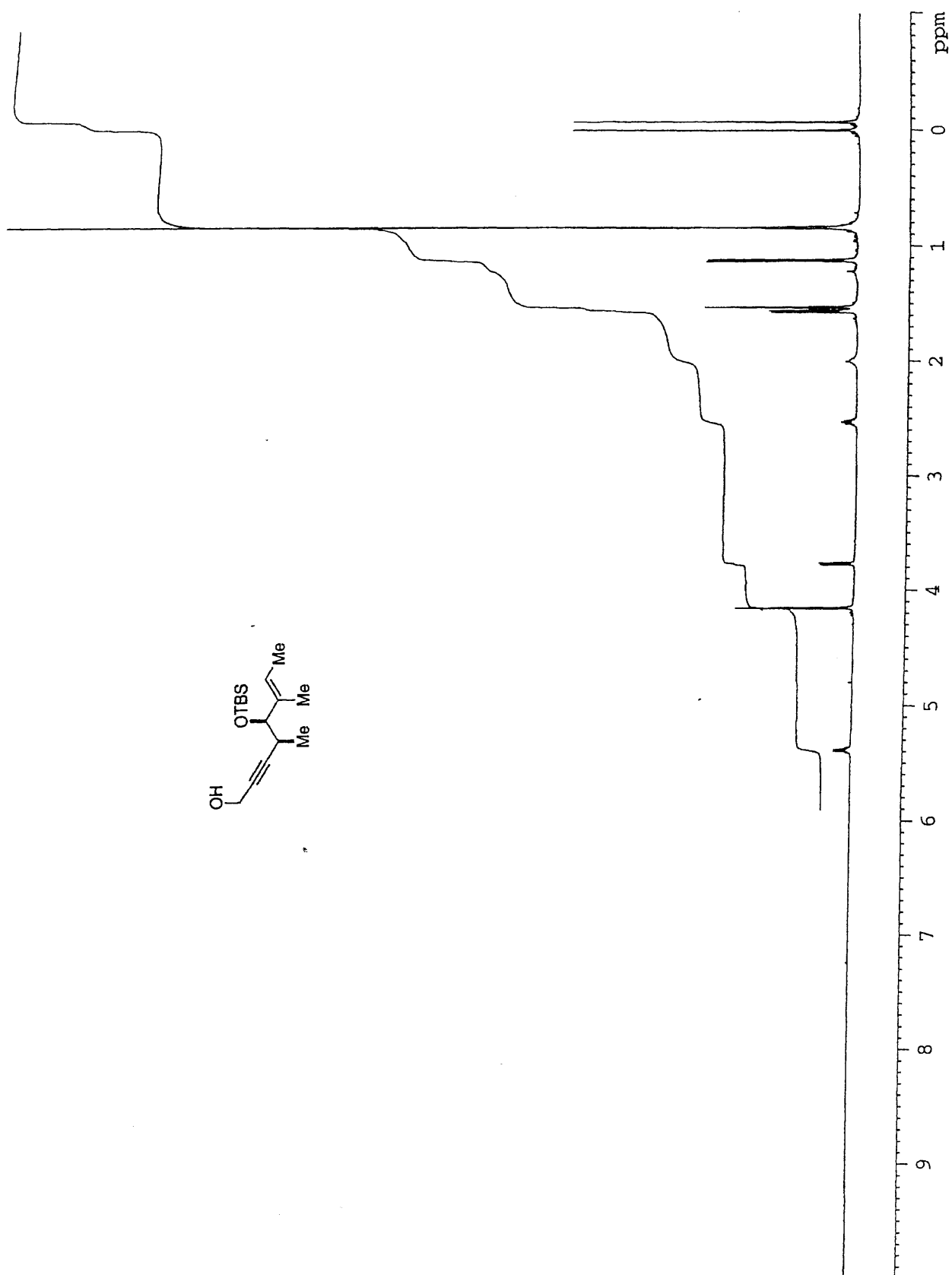
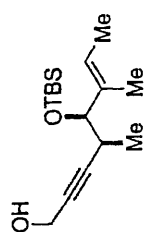


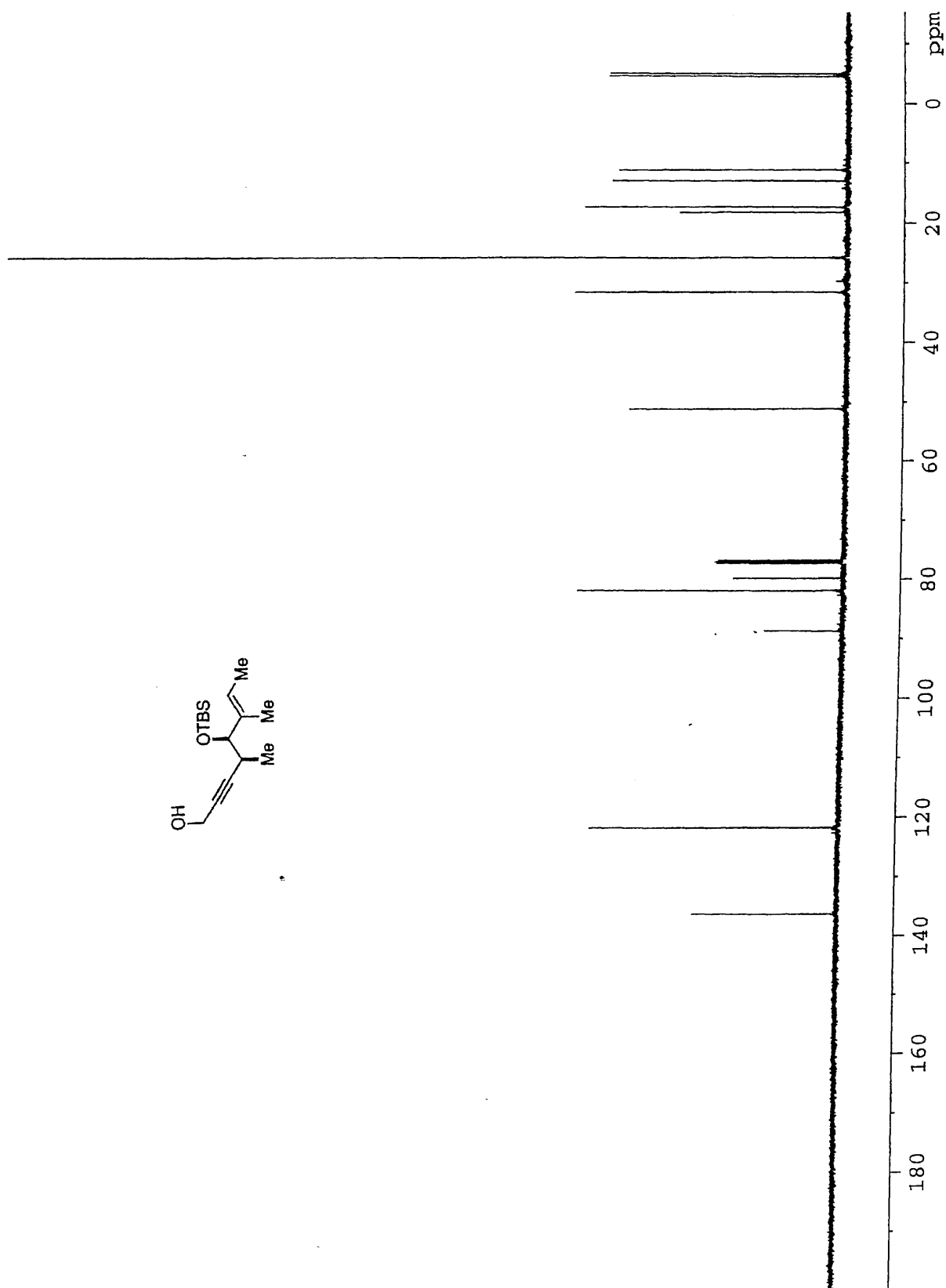
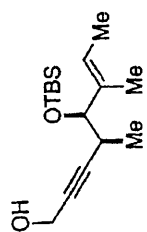


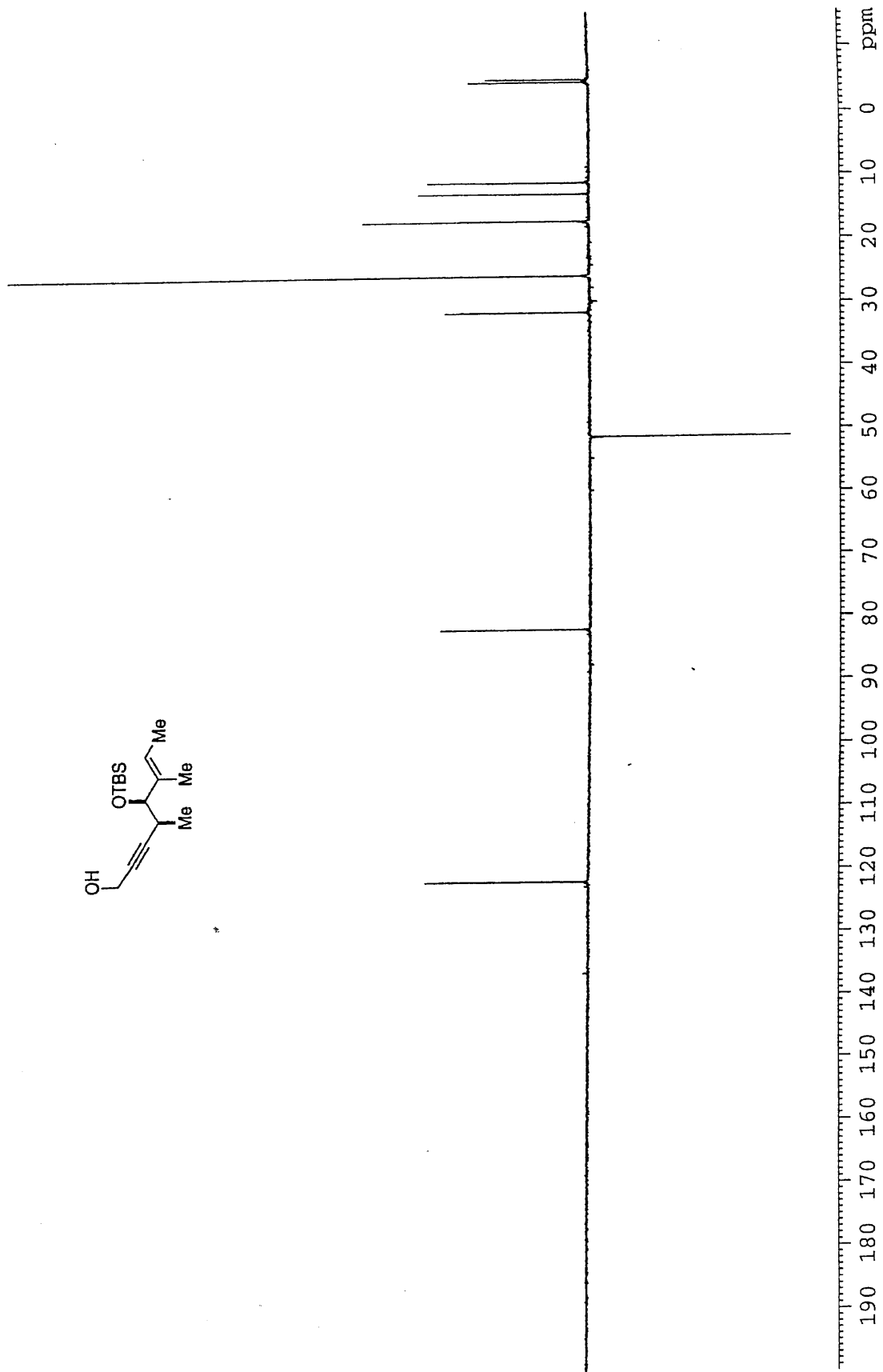
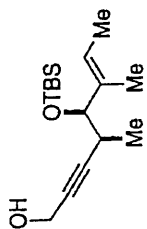


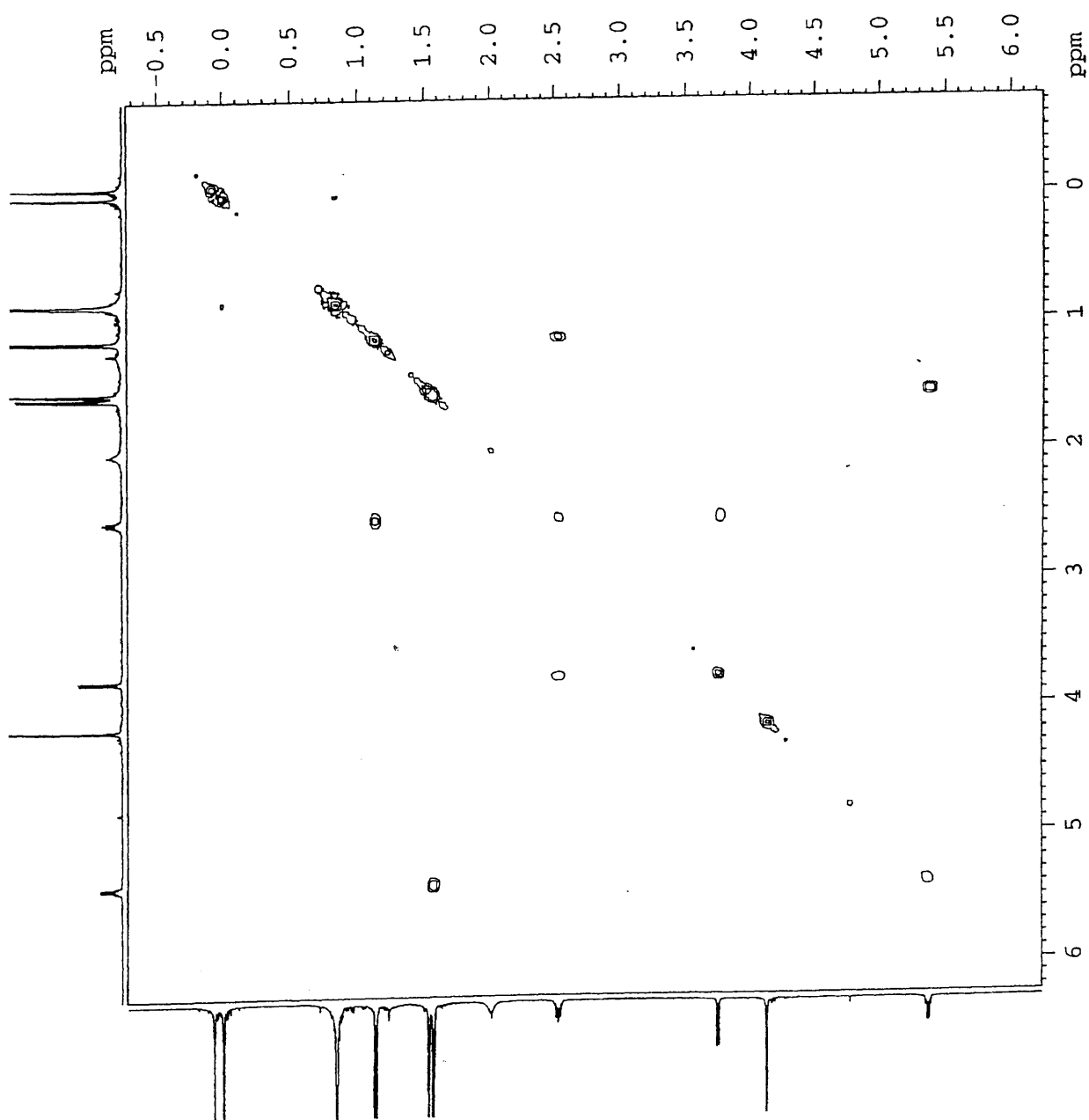
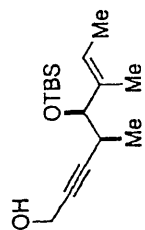


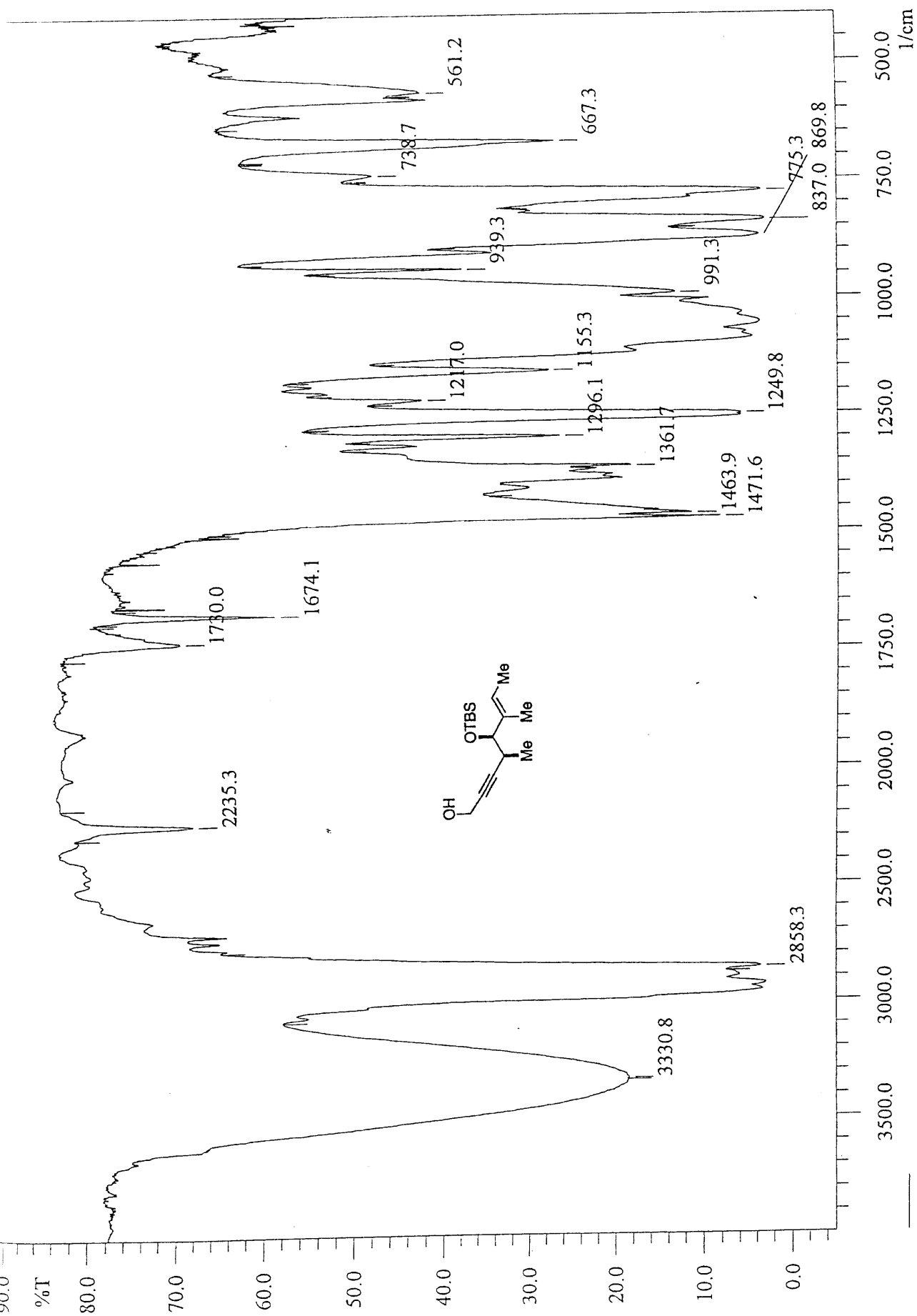














01060504: Scan 454 (83.18 min)

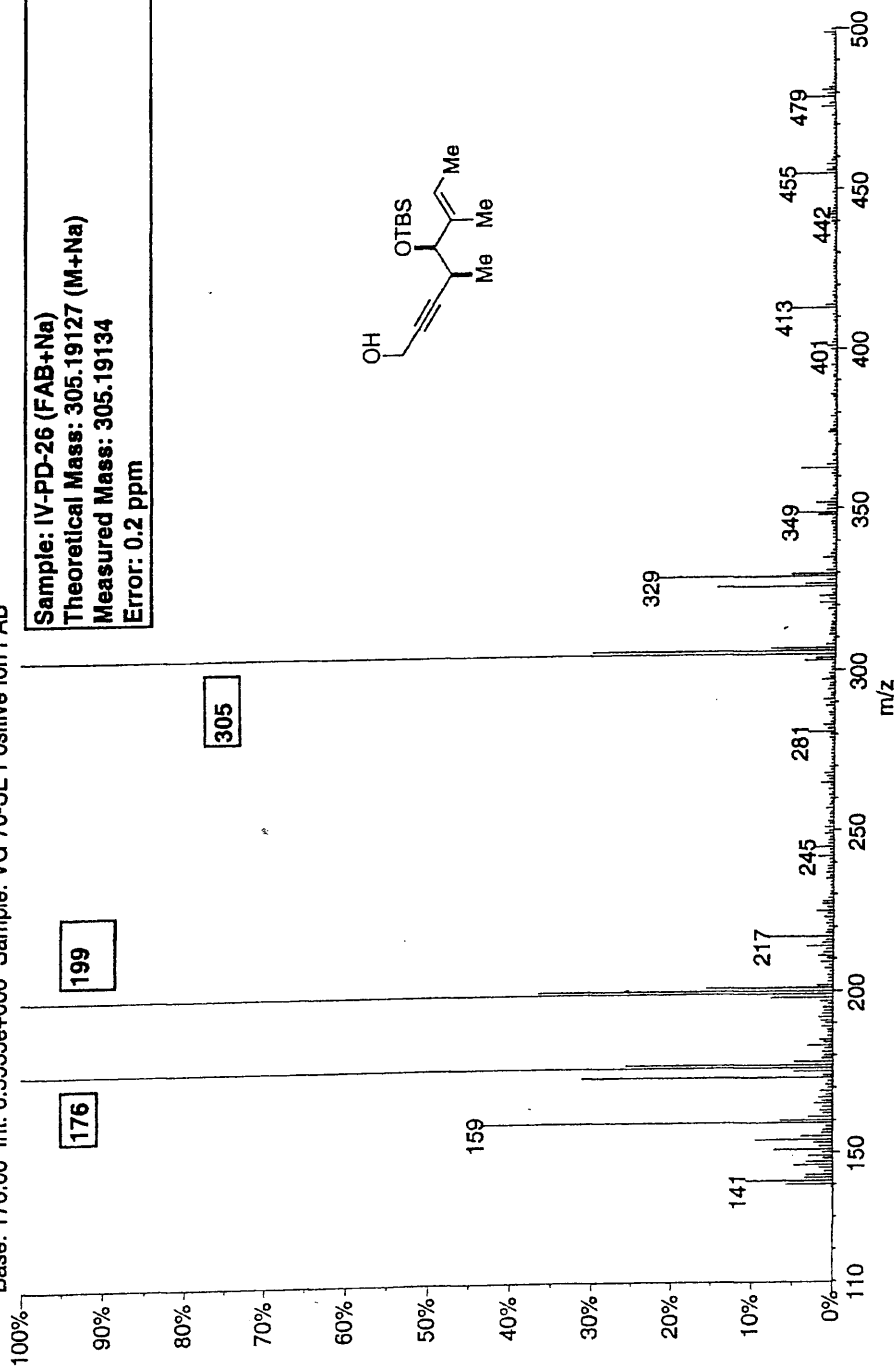
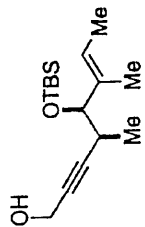
Base: 176.00 Int: 6.5535e+006 S

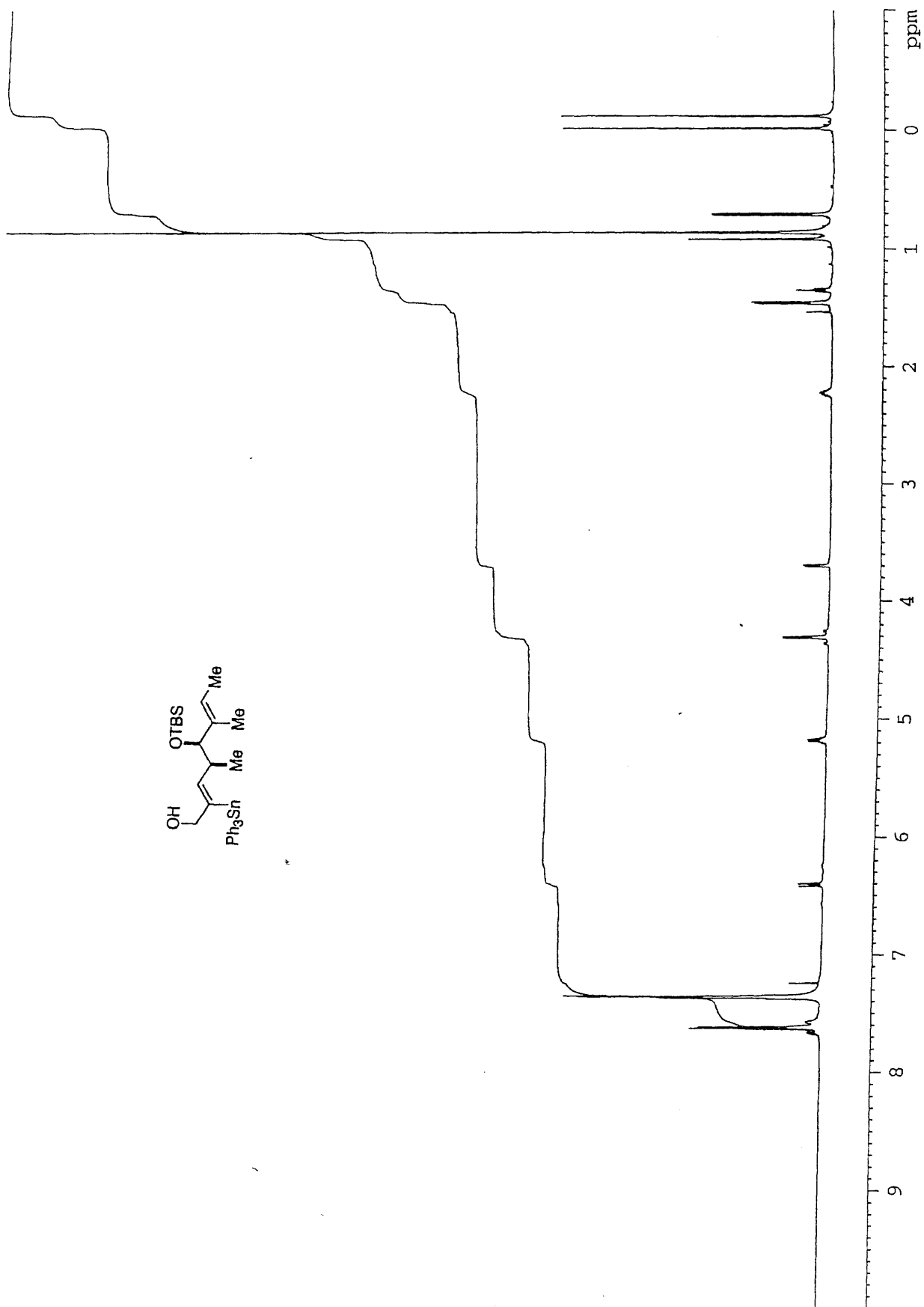
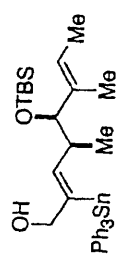
Sample: IV-PD-26 (EAB+Na)

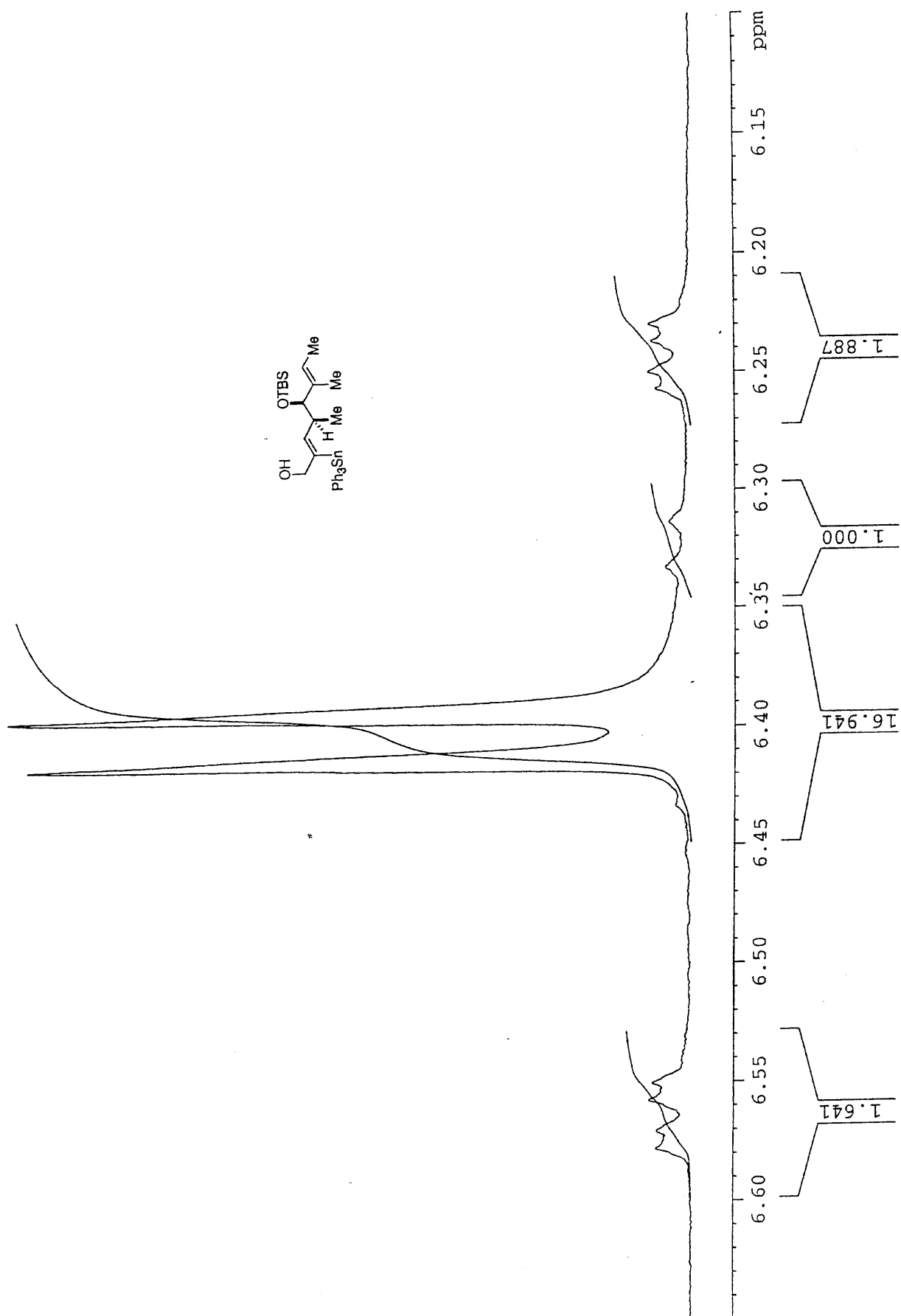
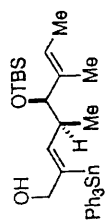
Theoretical Mass: 305.19127 (M+Na)

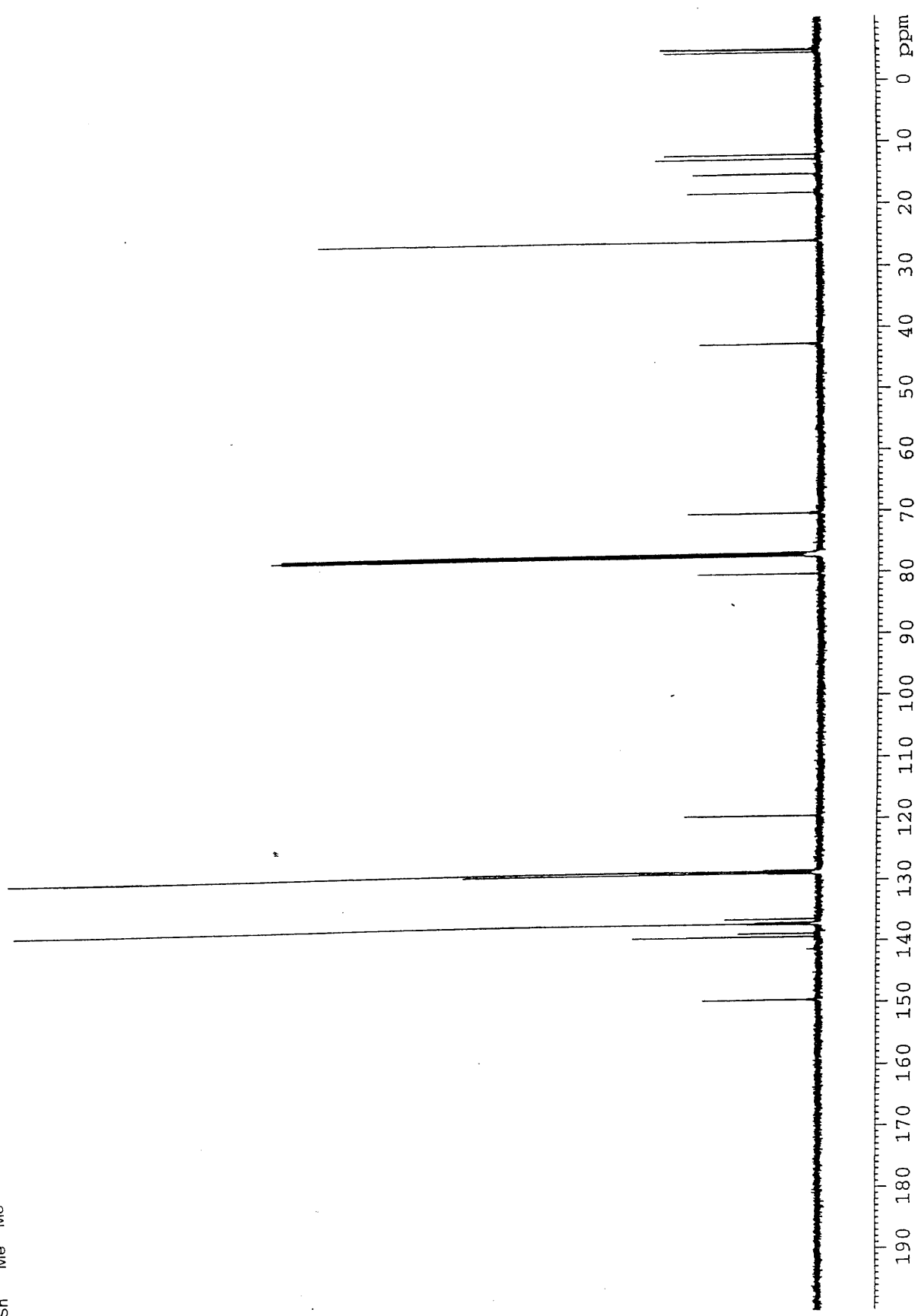
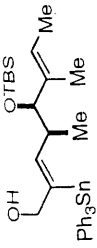
Measured Mass: 30E 10134

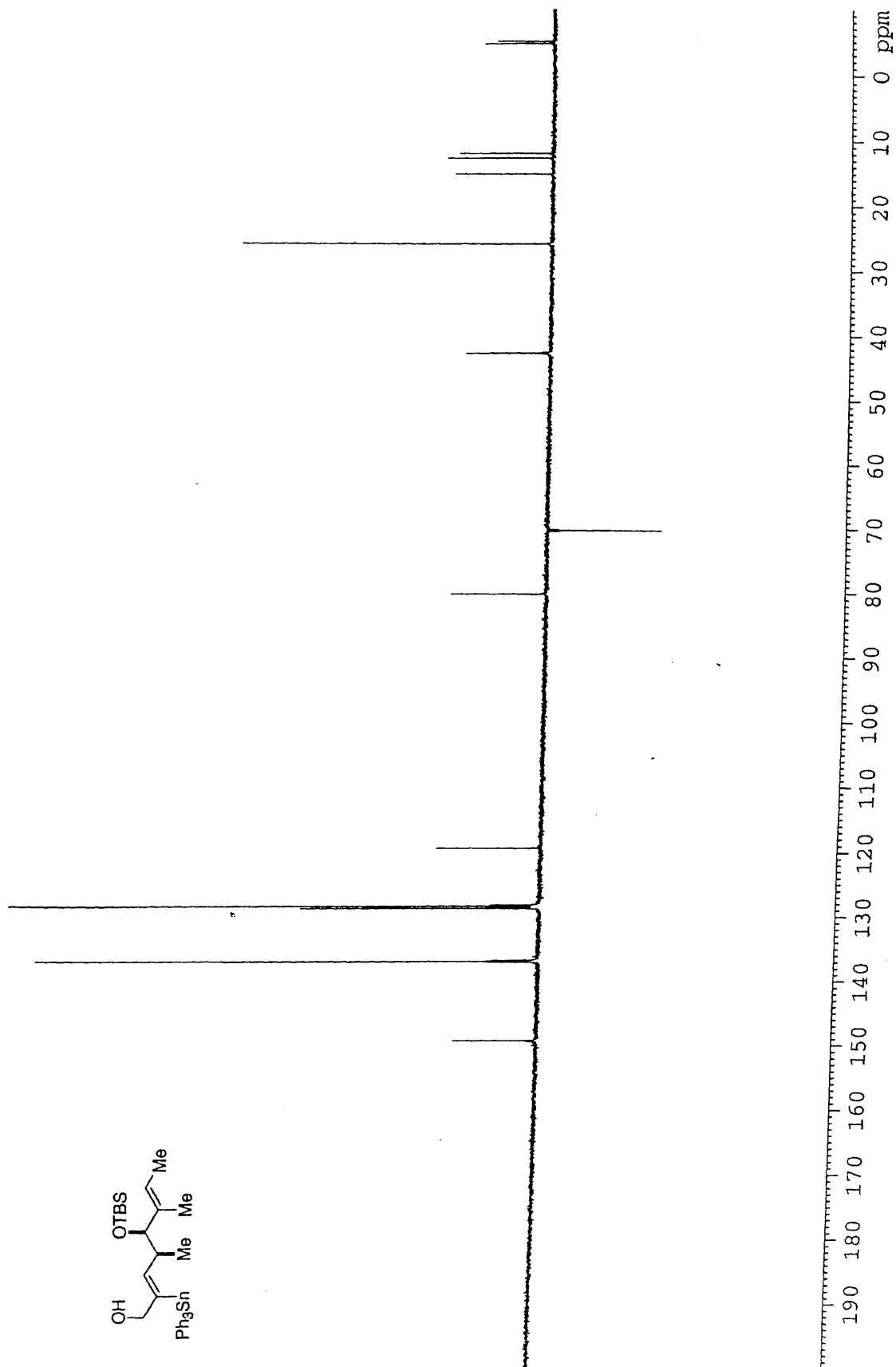
**Error: 02 mm**

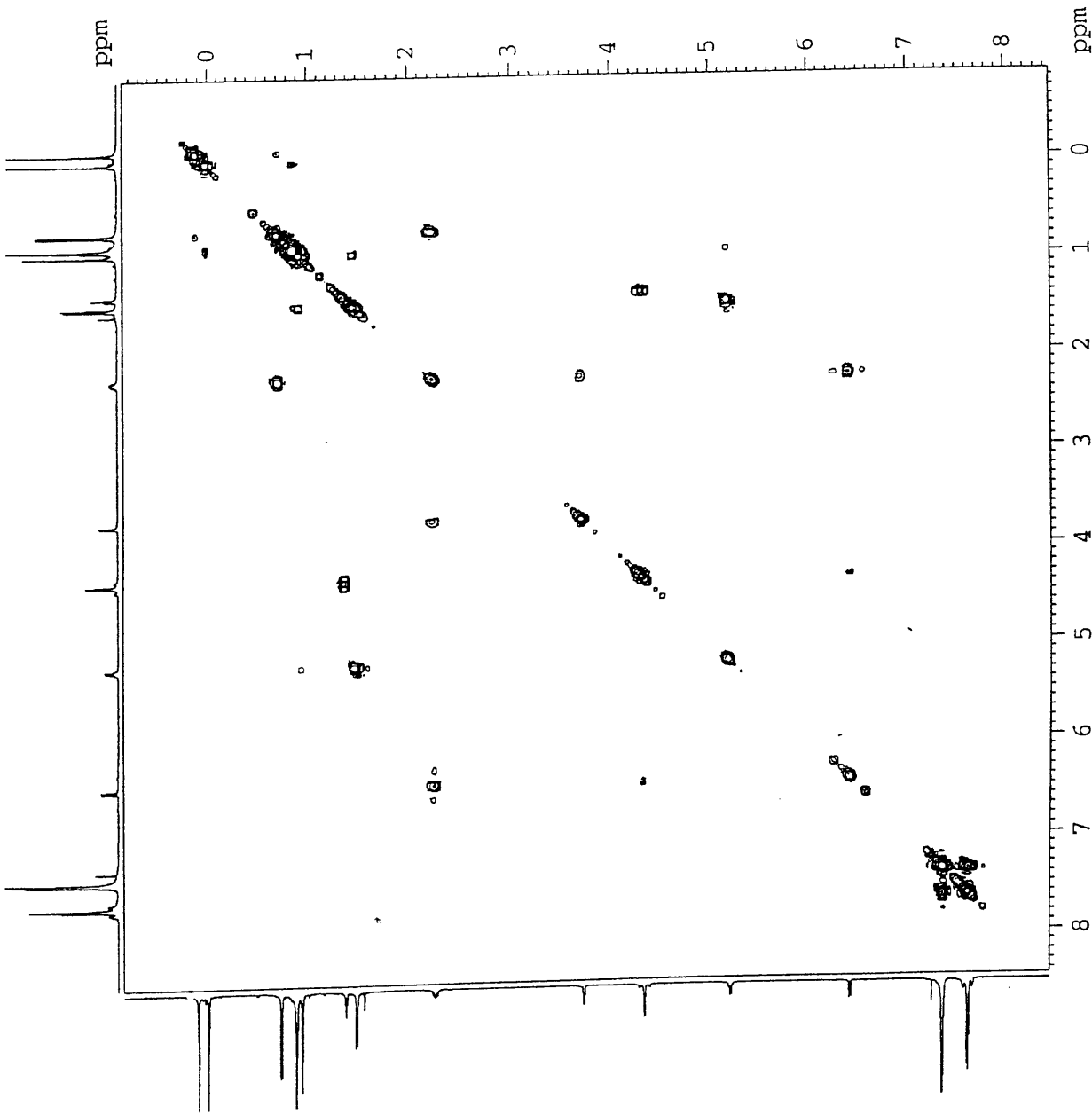


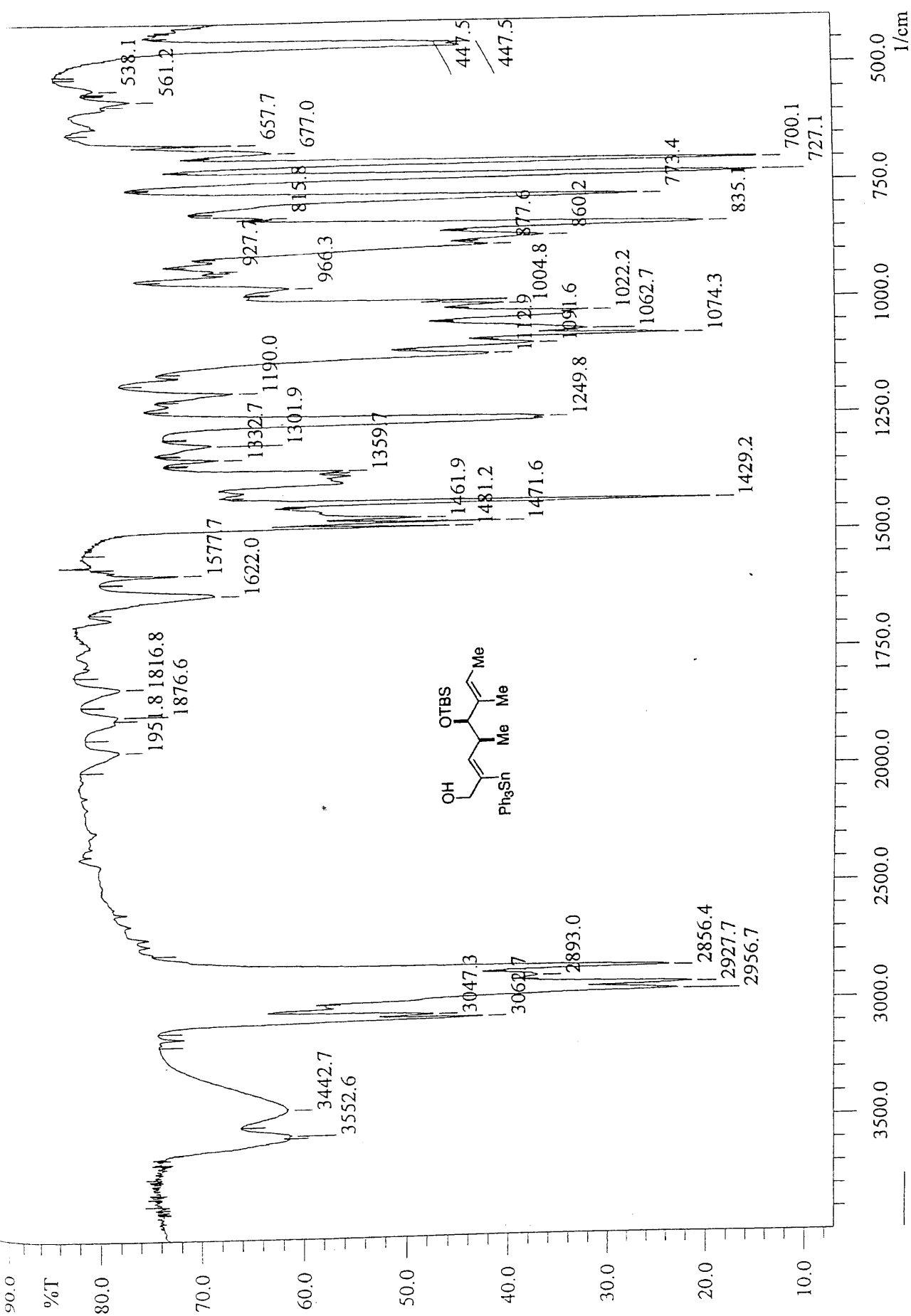






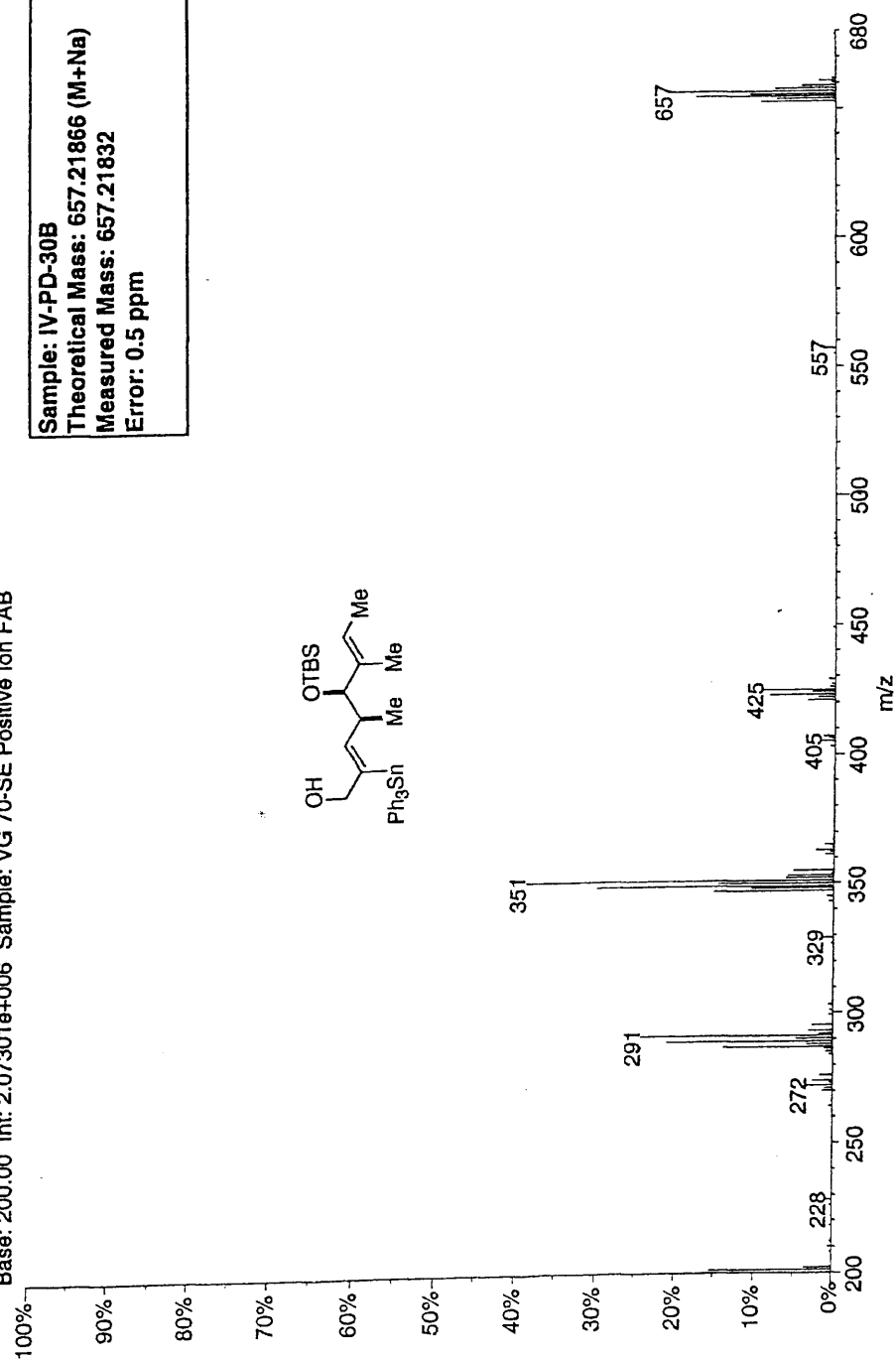
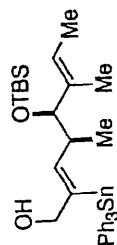




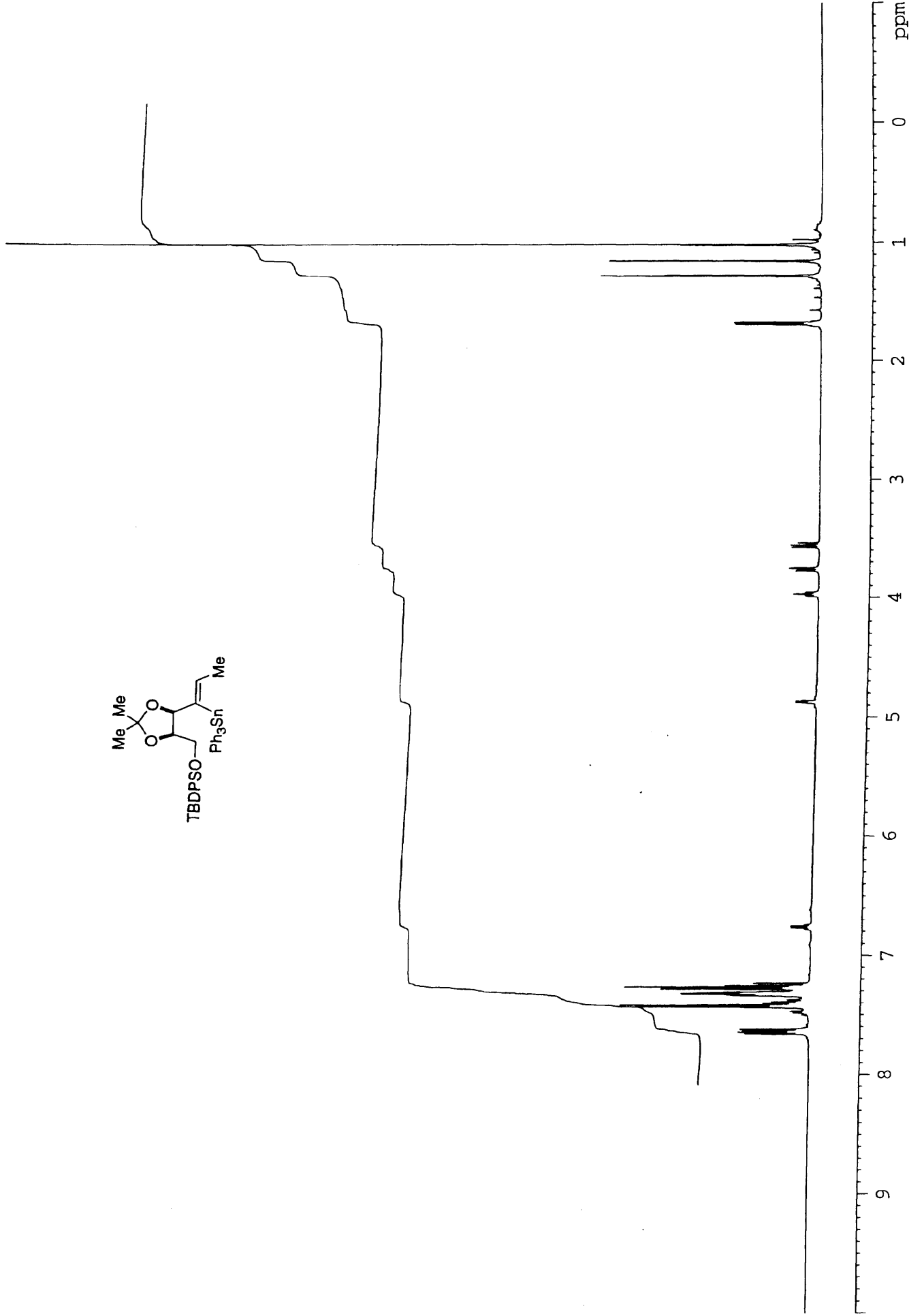


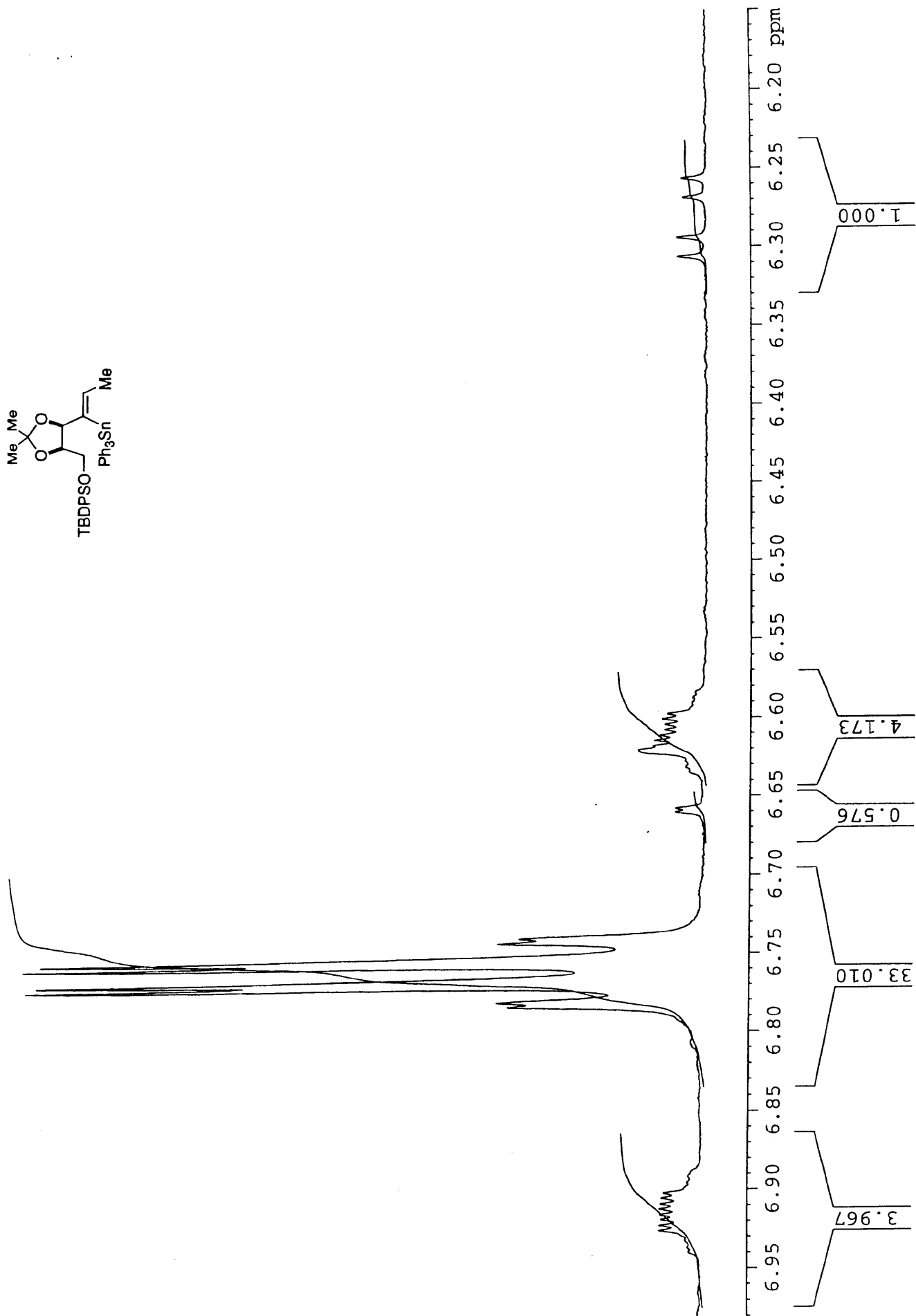
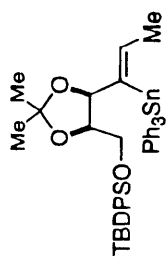
01170504: Scan Avg 559-560 (102.43 - 102.62 min)  
Base: 200.00 Int: 2.07301e+006 Sample: VG 70-SE Positive Ion FAB

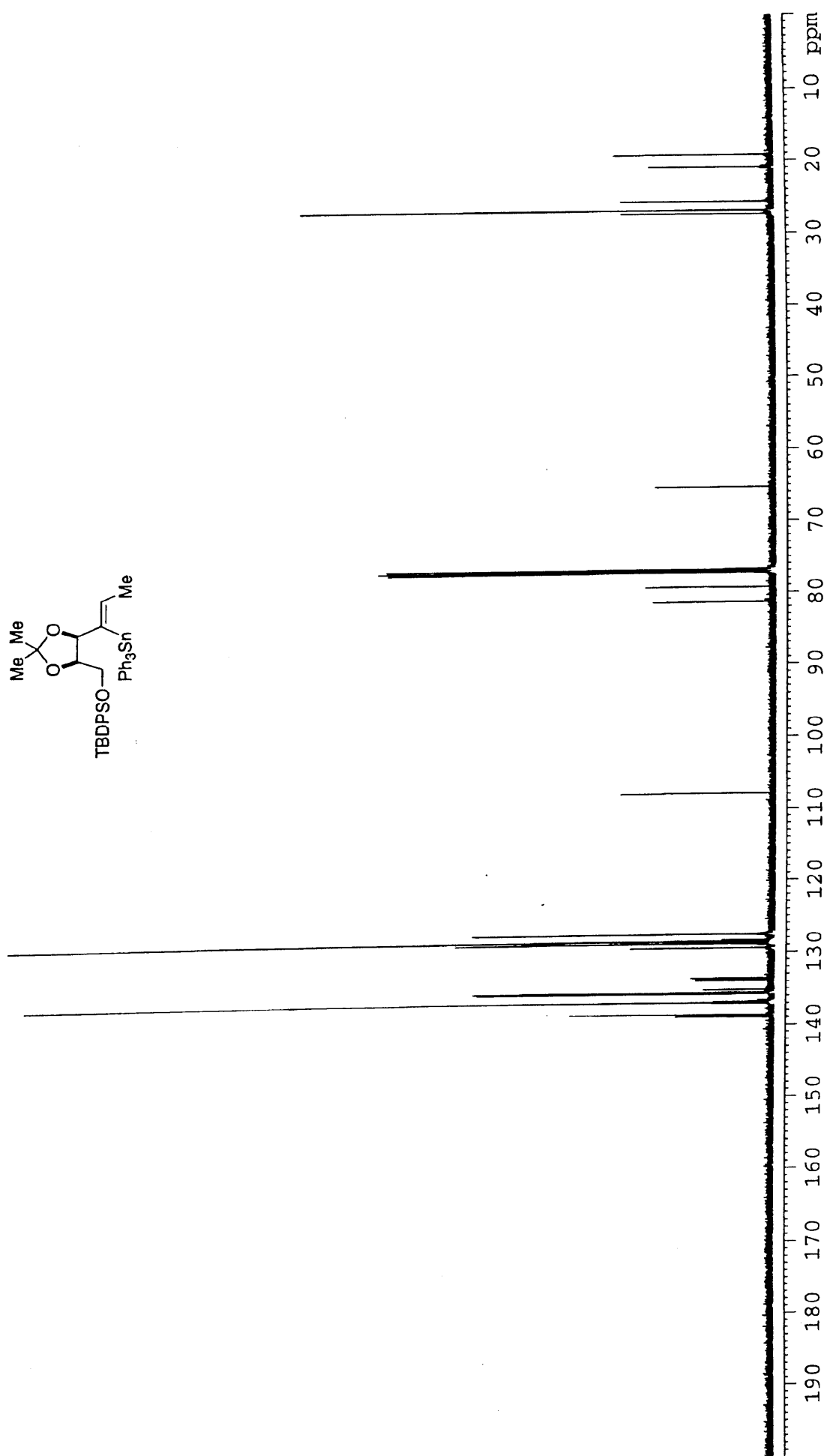
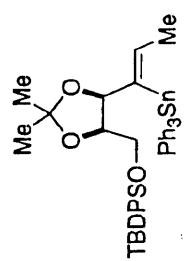
Sample: IV-PD-30B  
Theoretical Mass: 657.21866 (M+Na)  
Measured Mass: 657.21832  
Error: 0.5 ppm

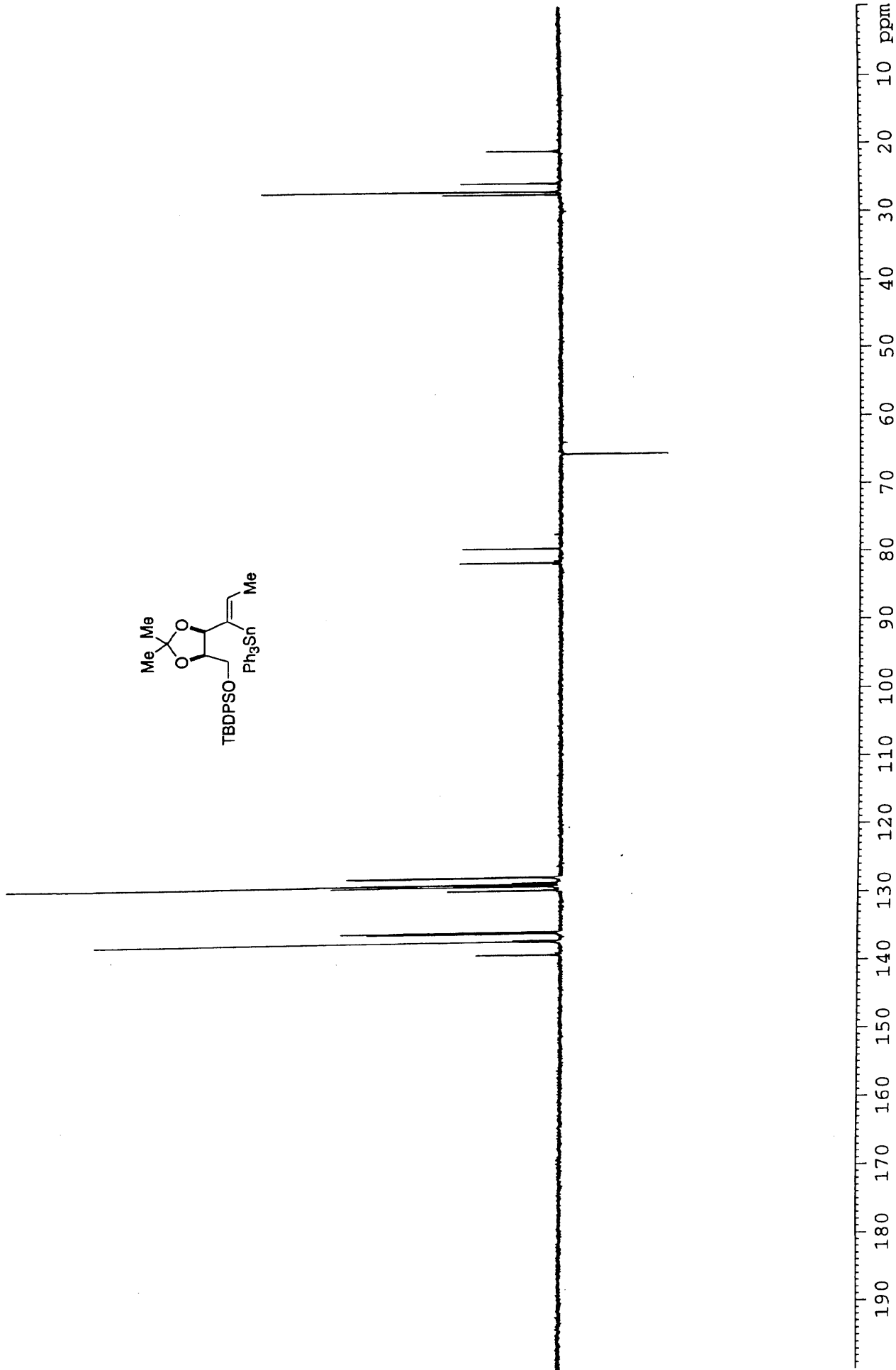


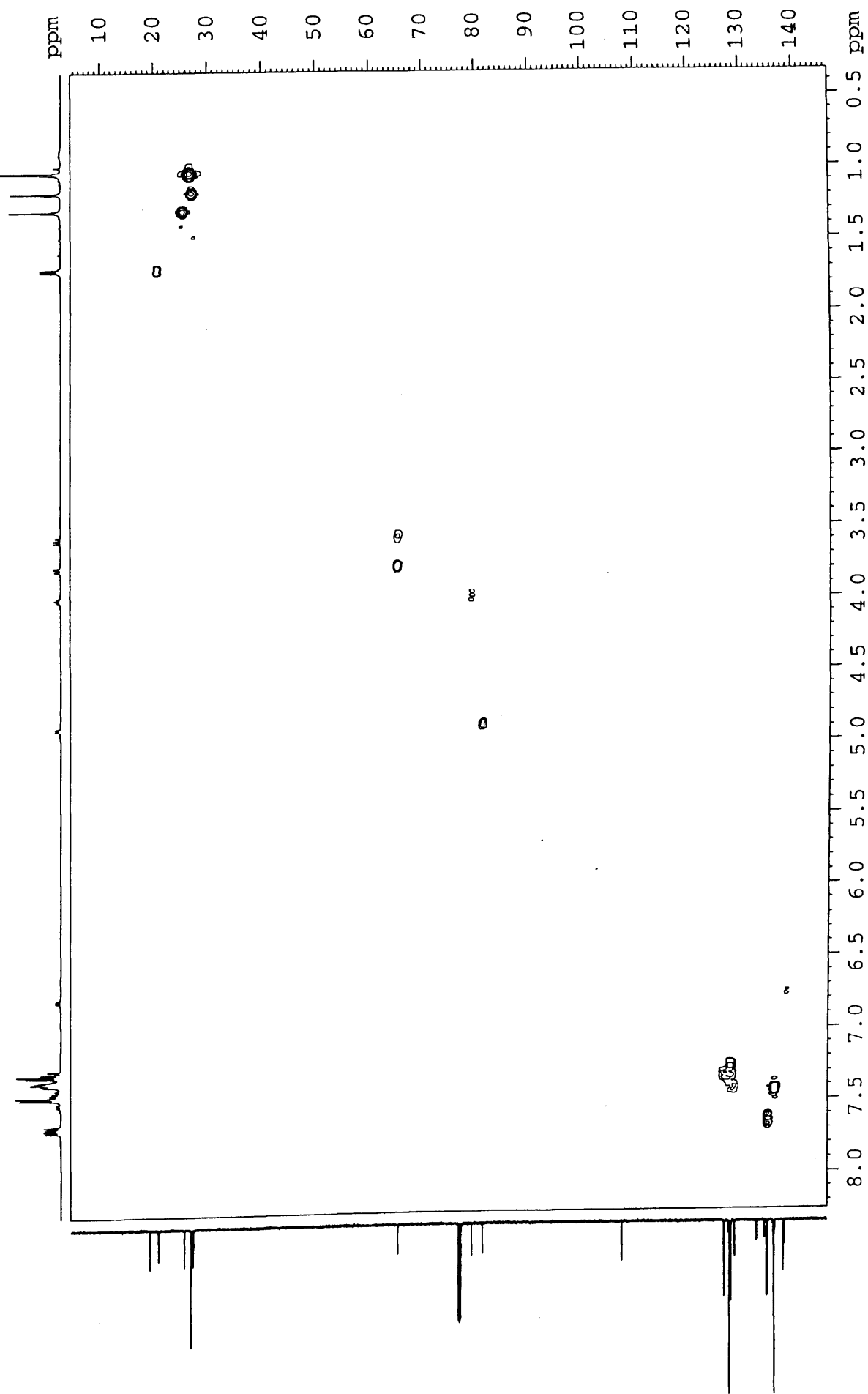
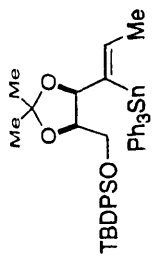


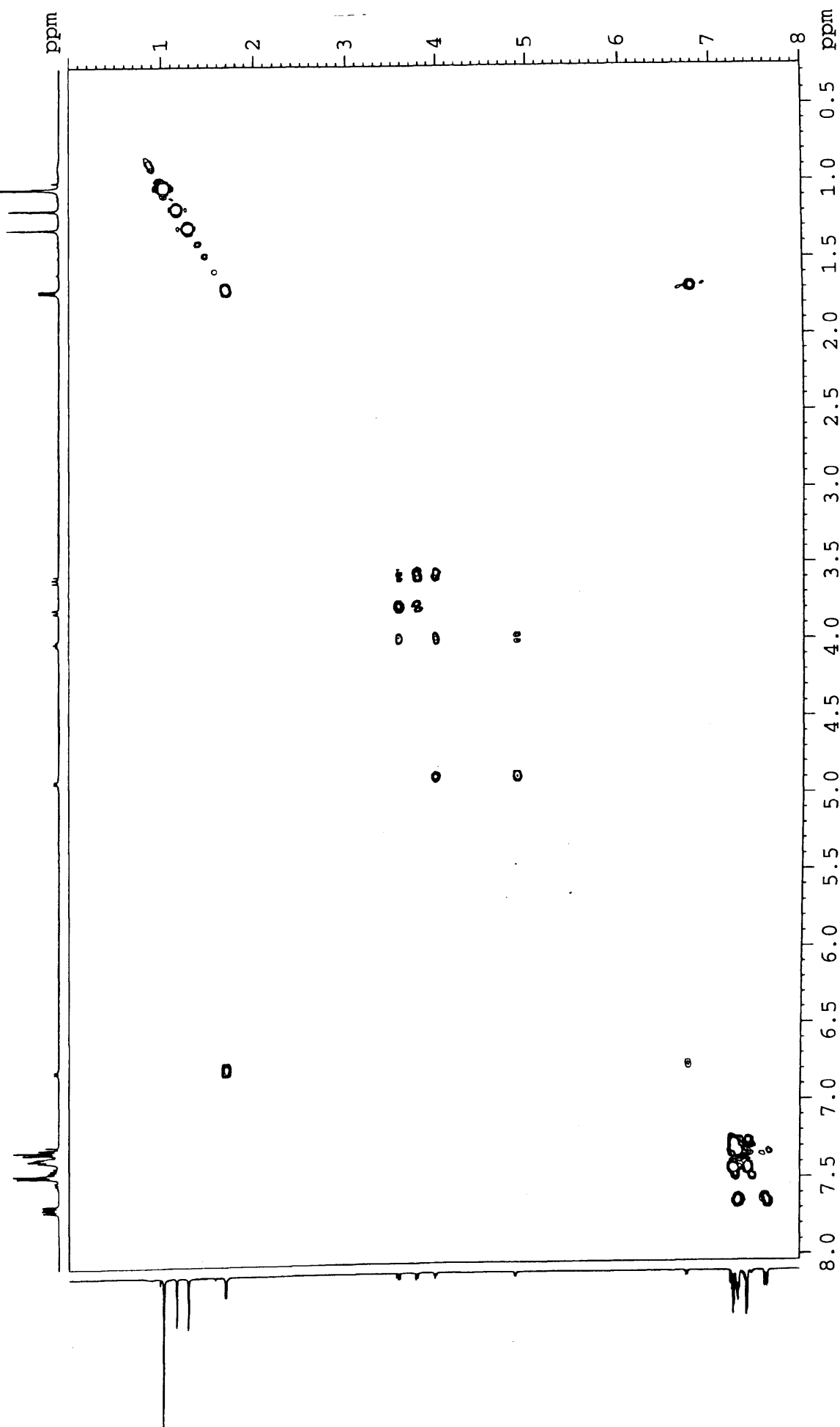
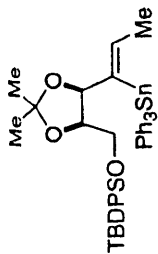


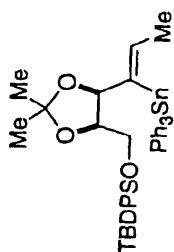
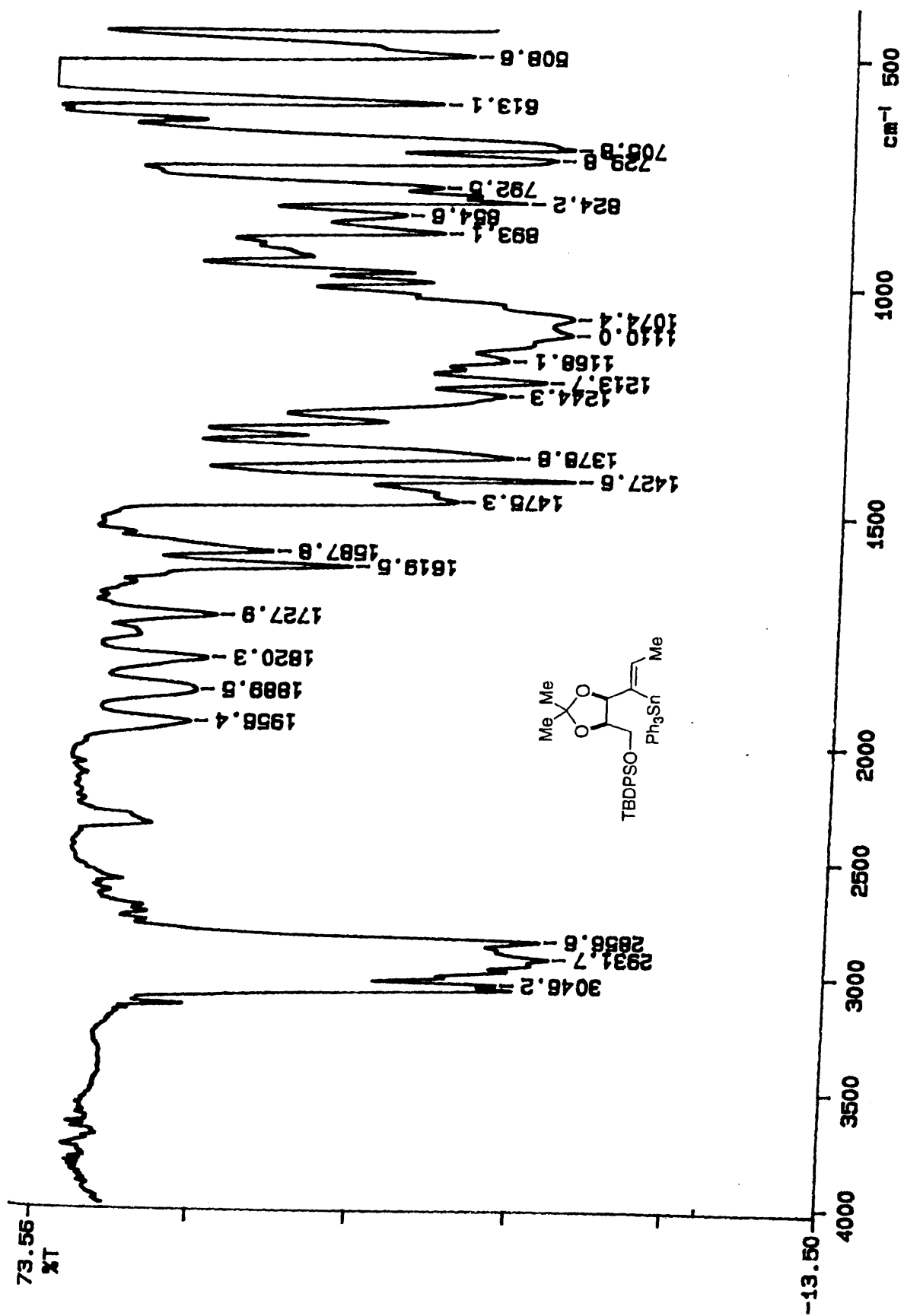




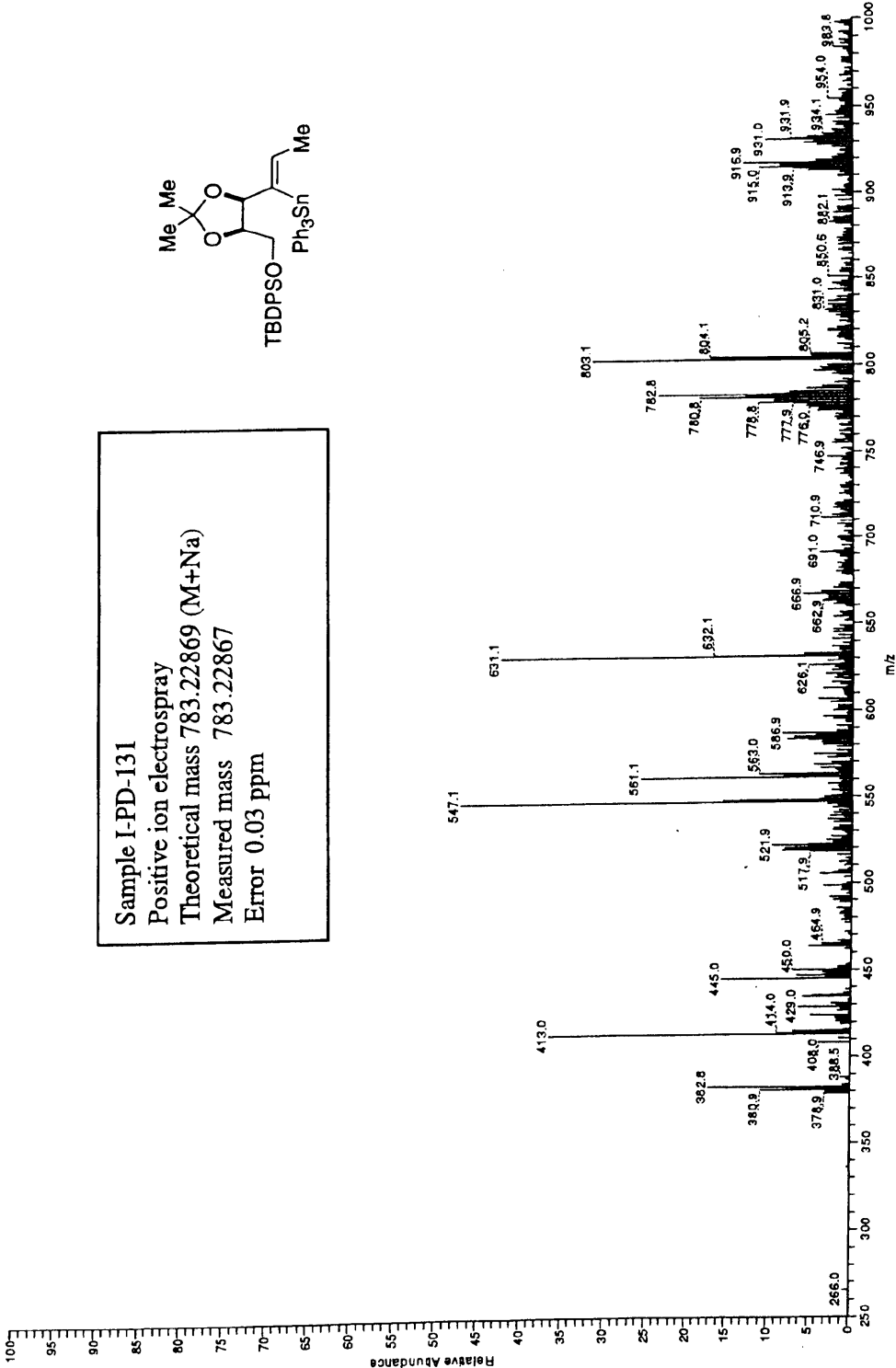
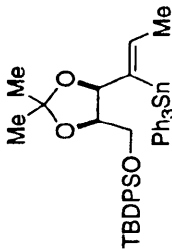




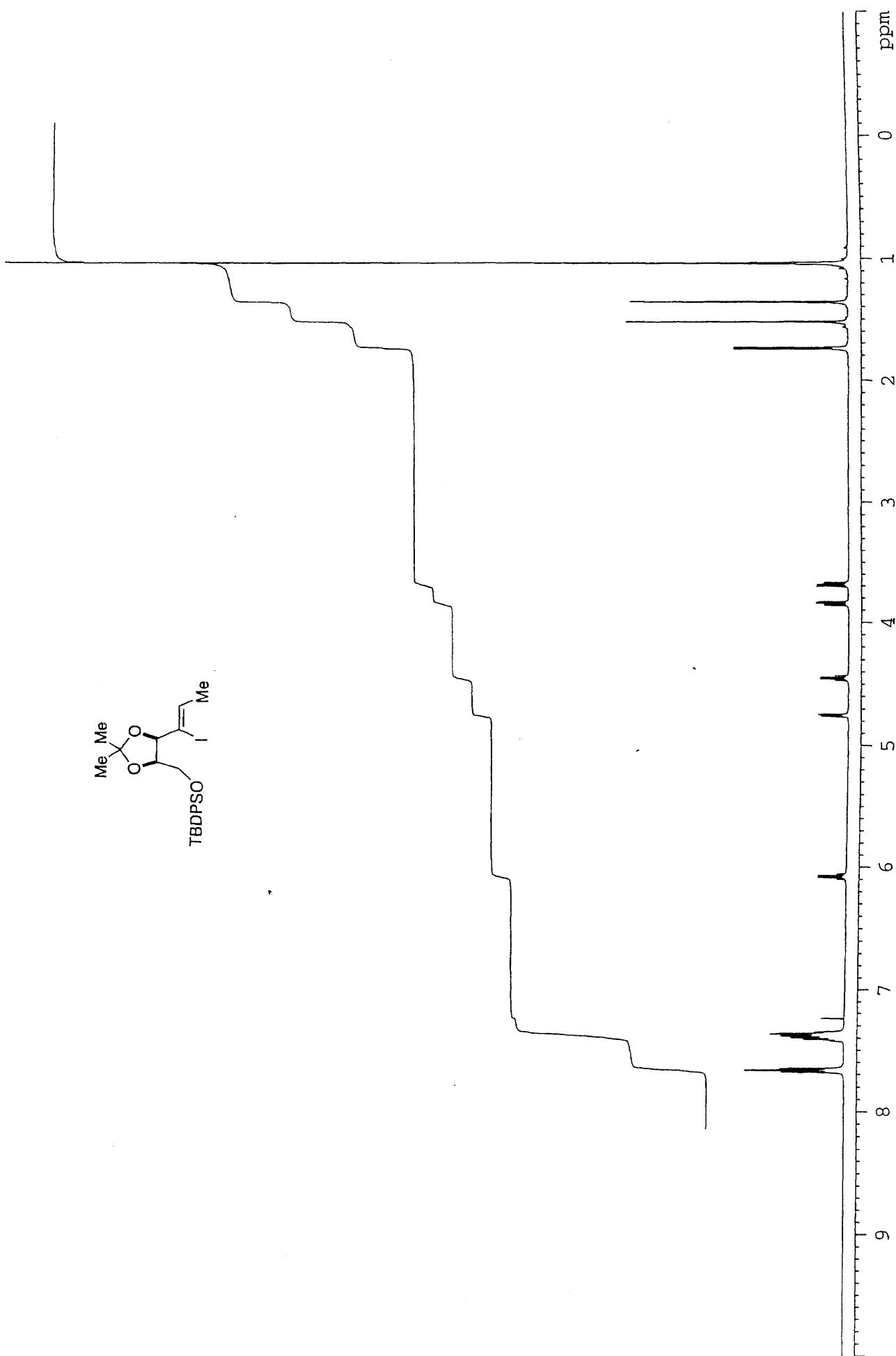
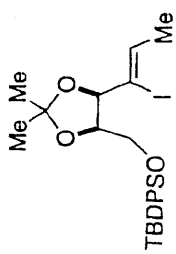


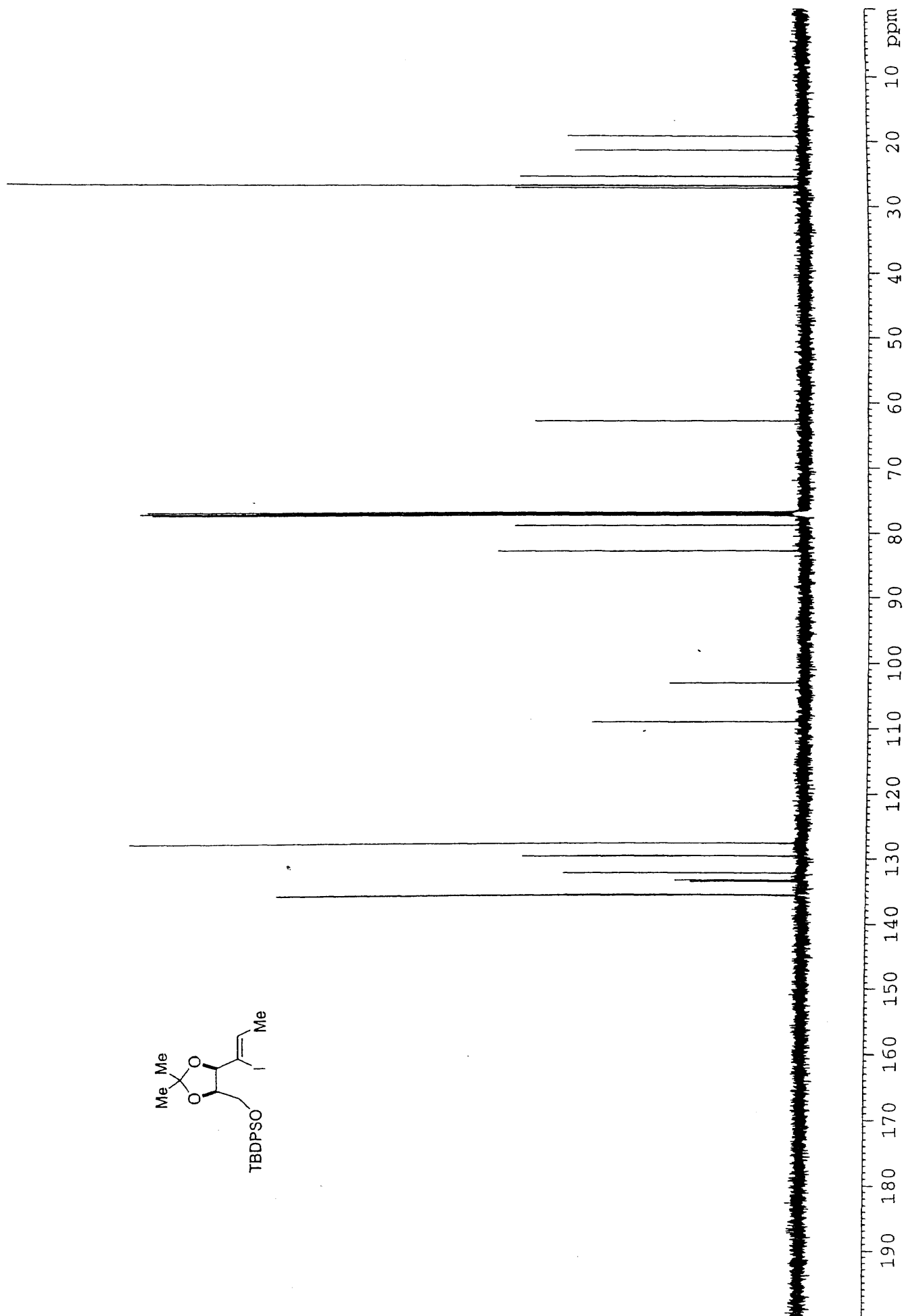
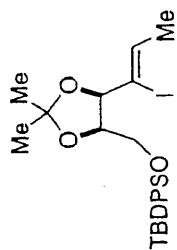


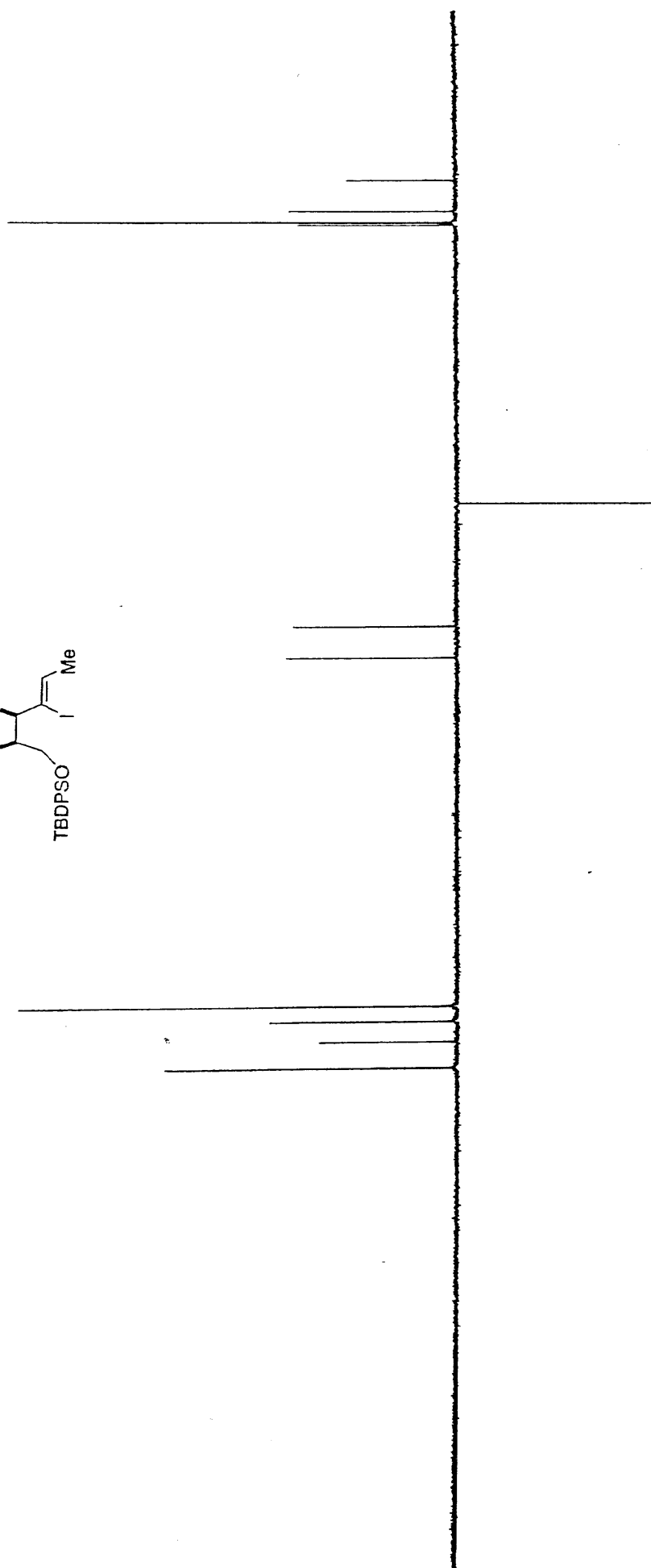
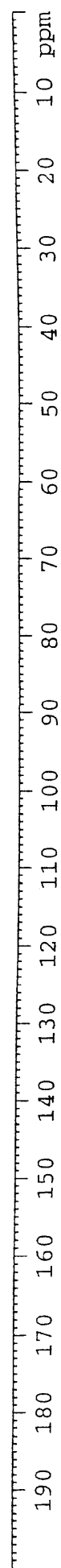
Sample I-PD-131  
Positive ion electrospray  
Theoretical mass 783.22869 (M+Na)  
Measured mass 783.22867  
Error 0.03 ppm

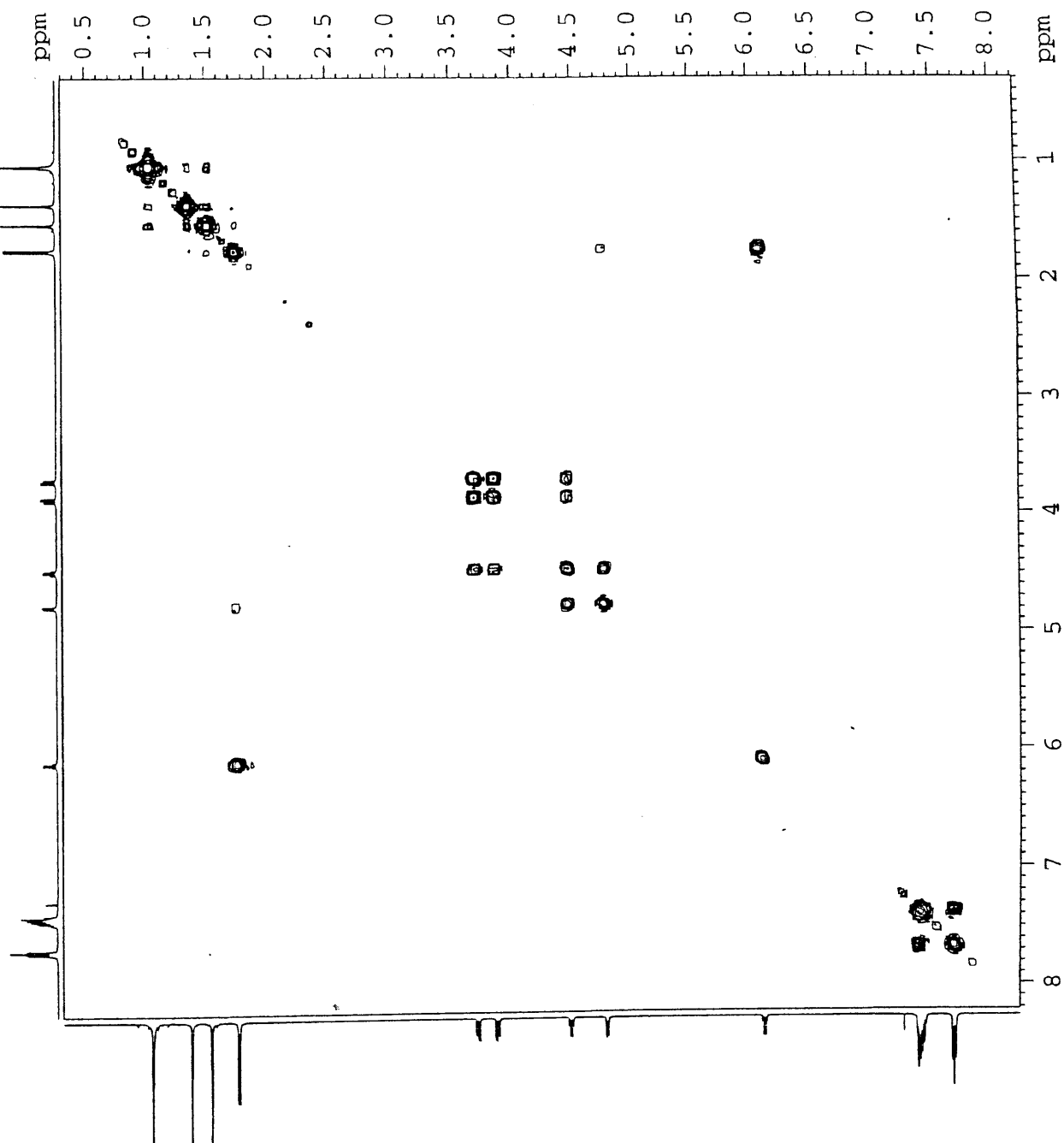
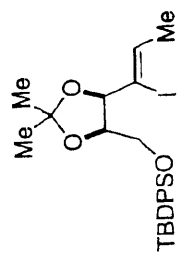


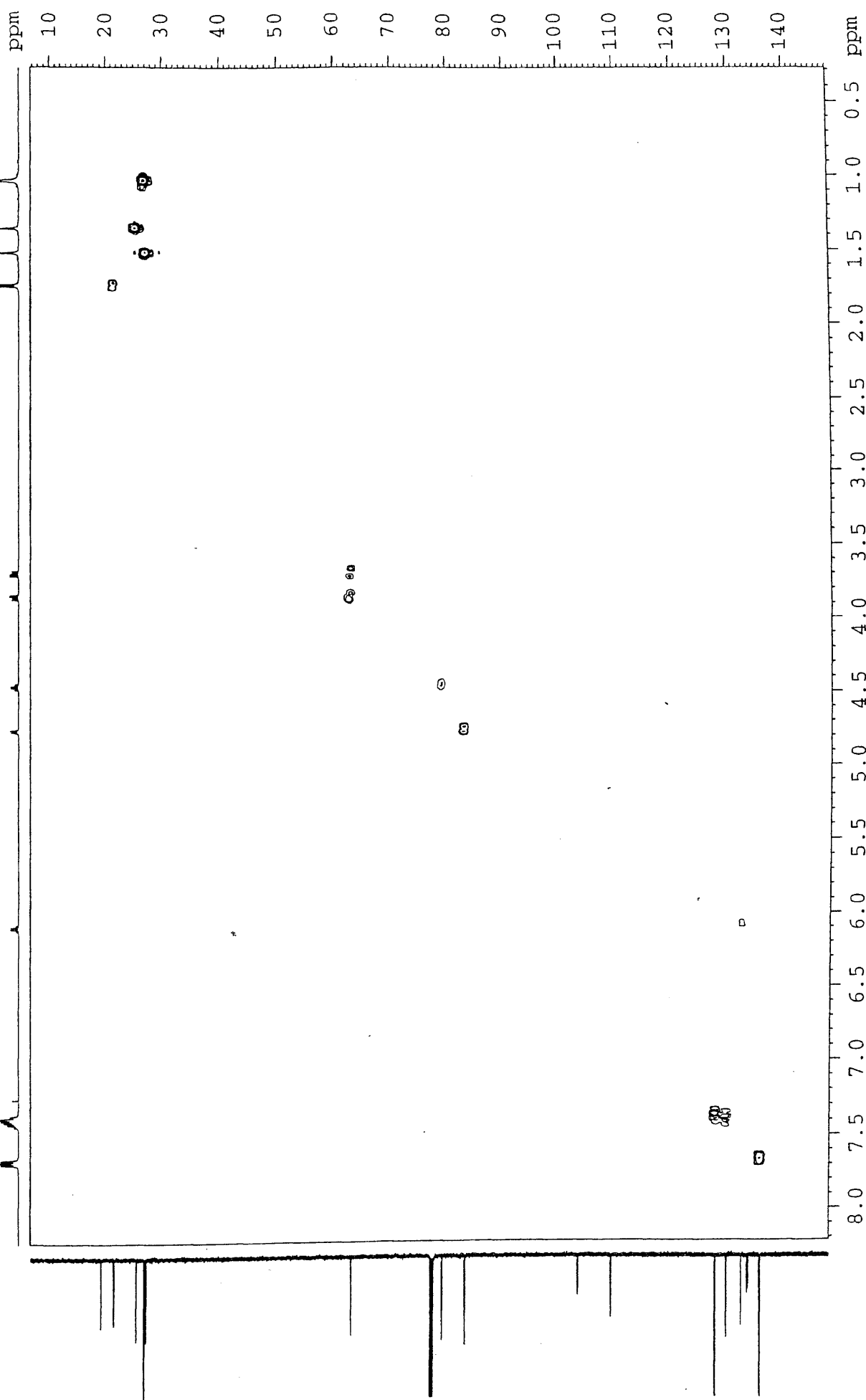
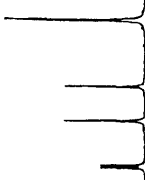


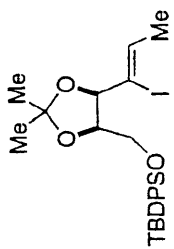
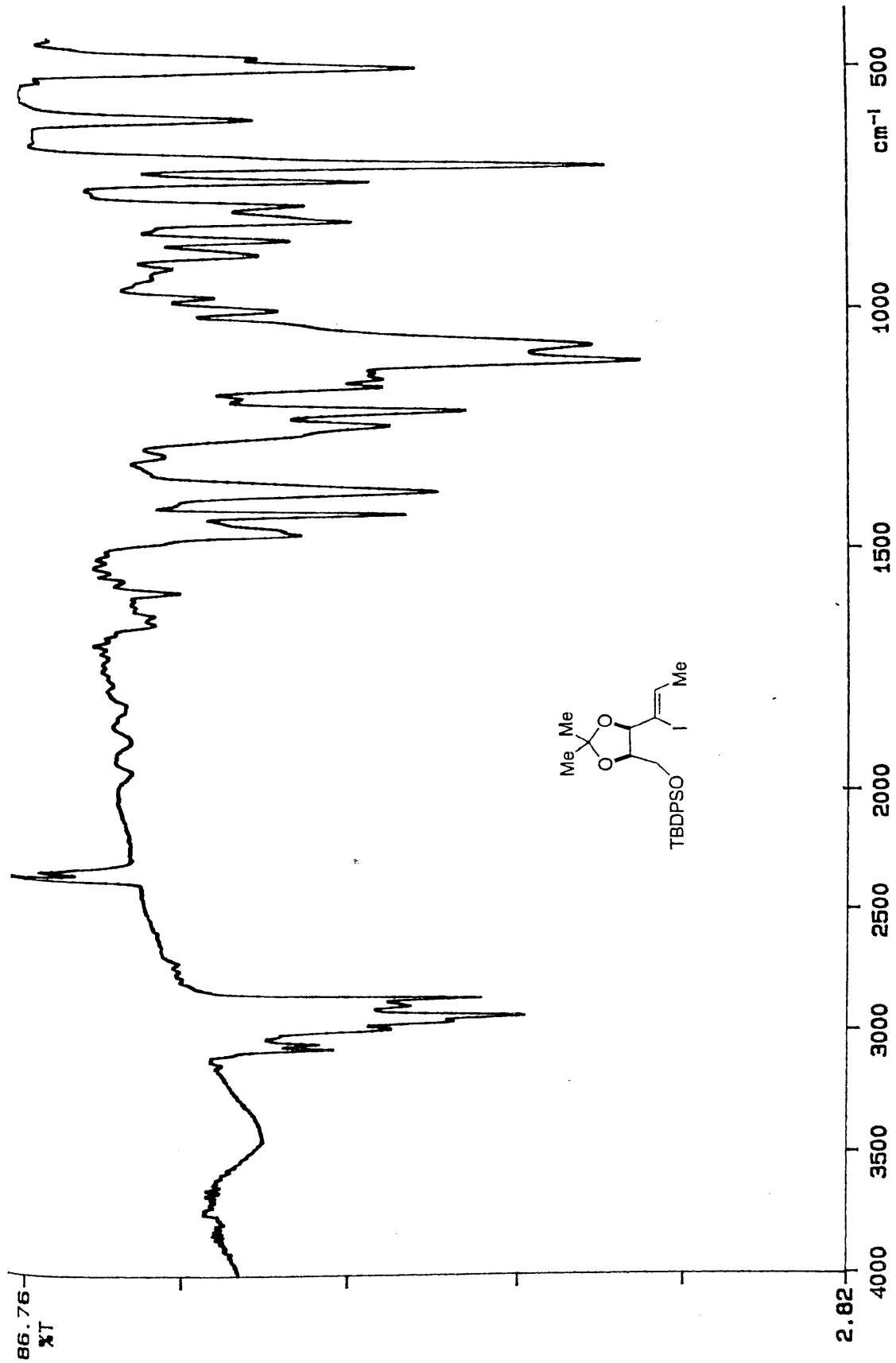




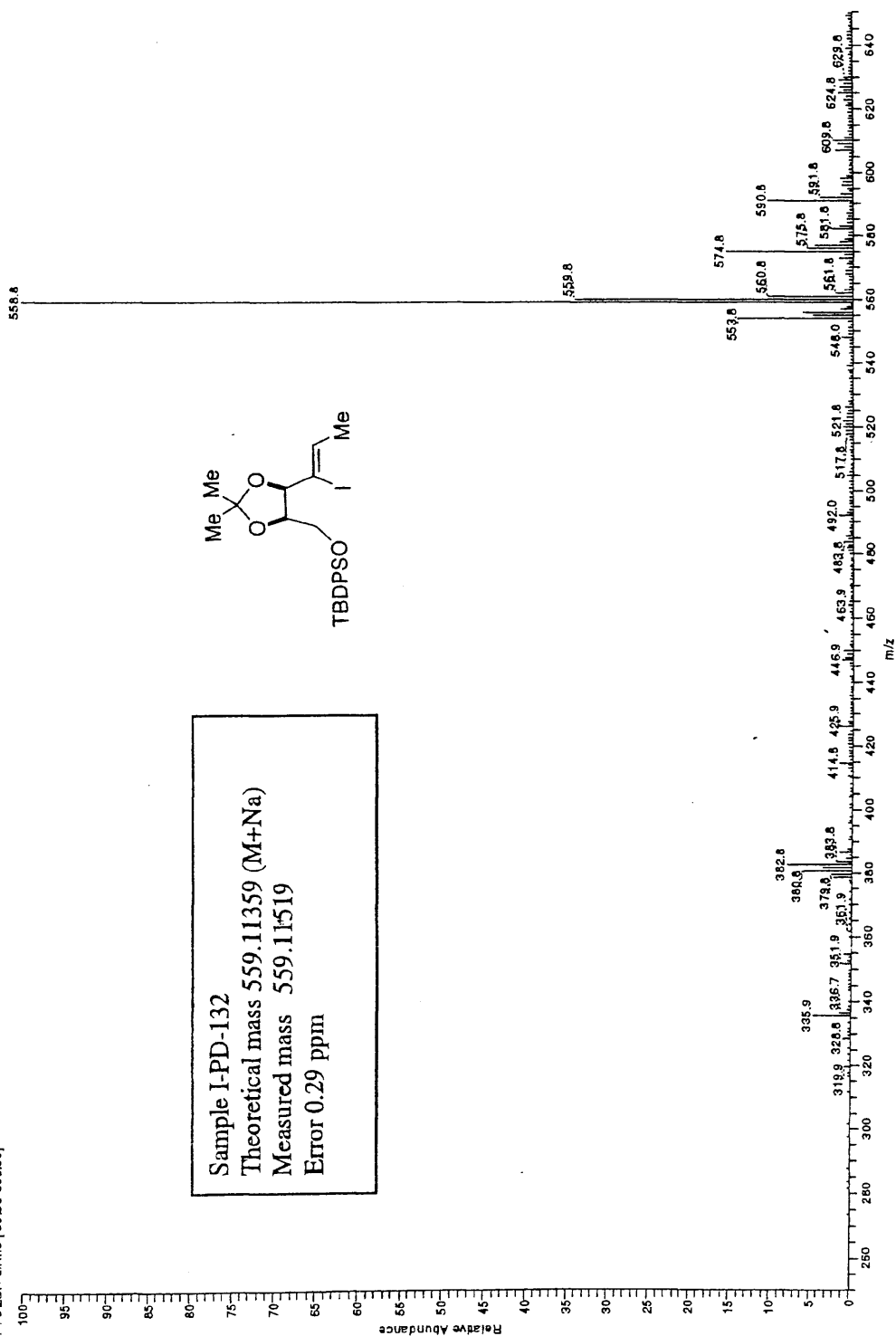


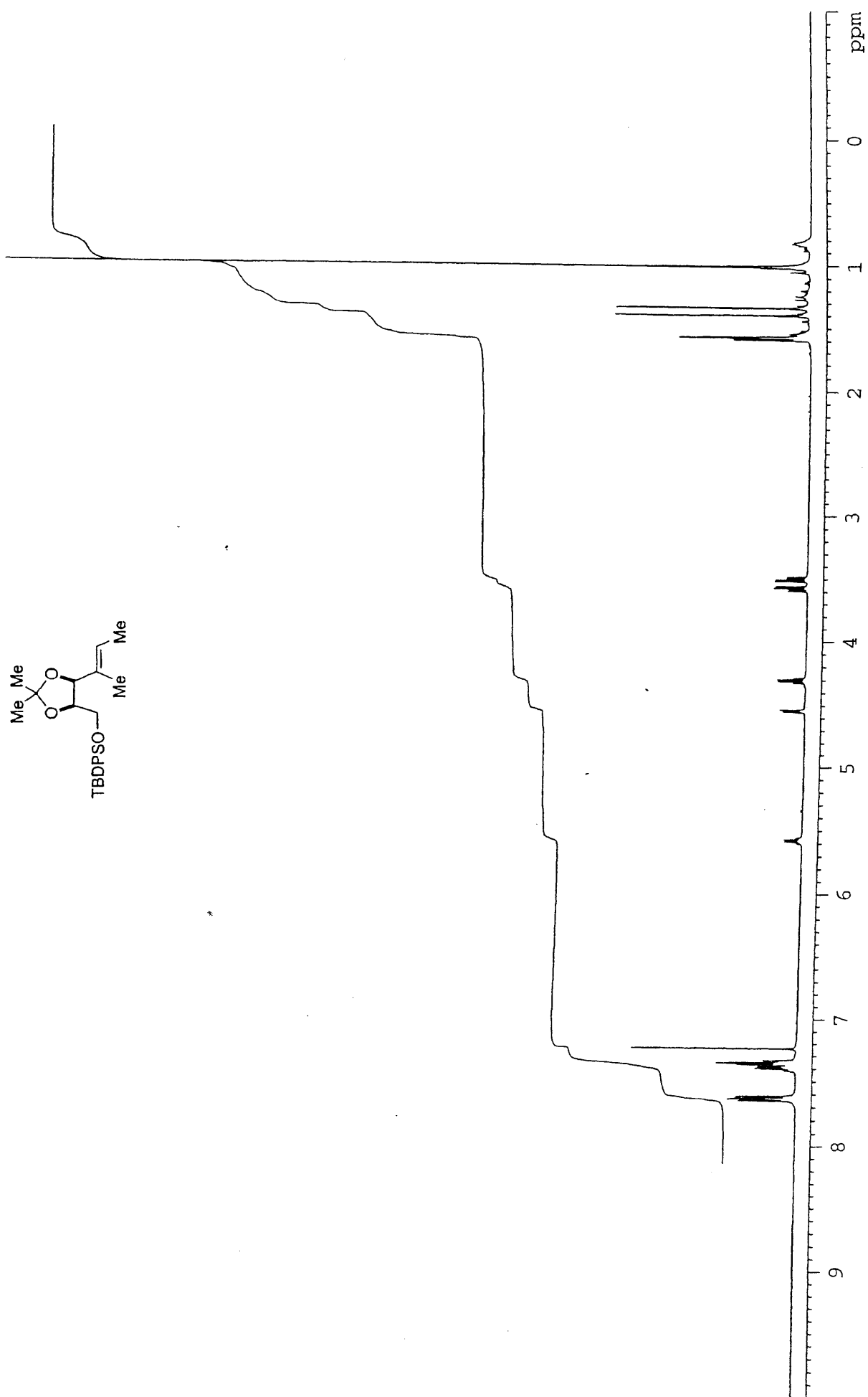
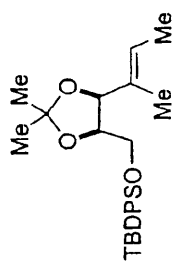




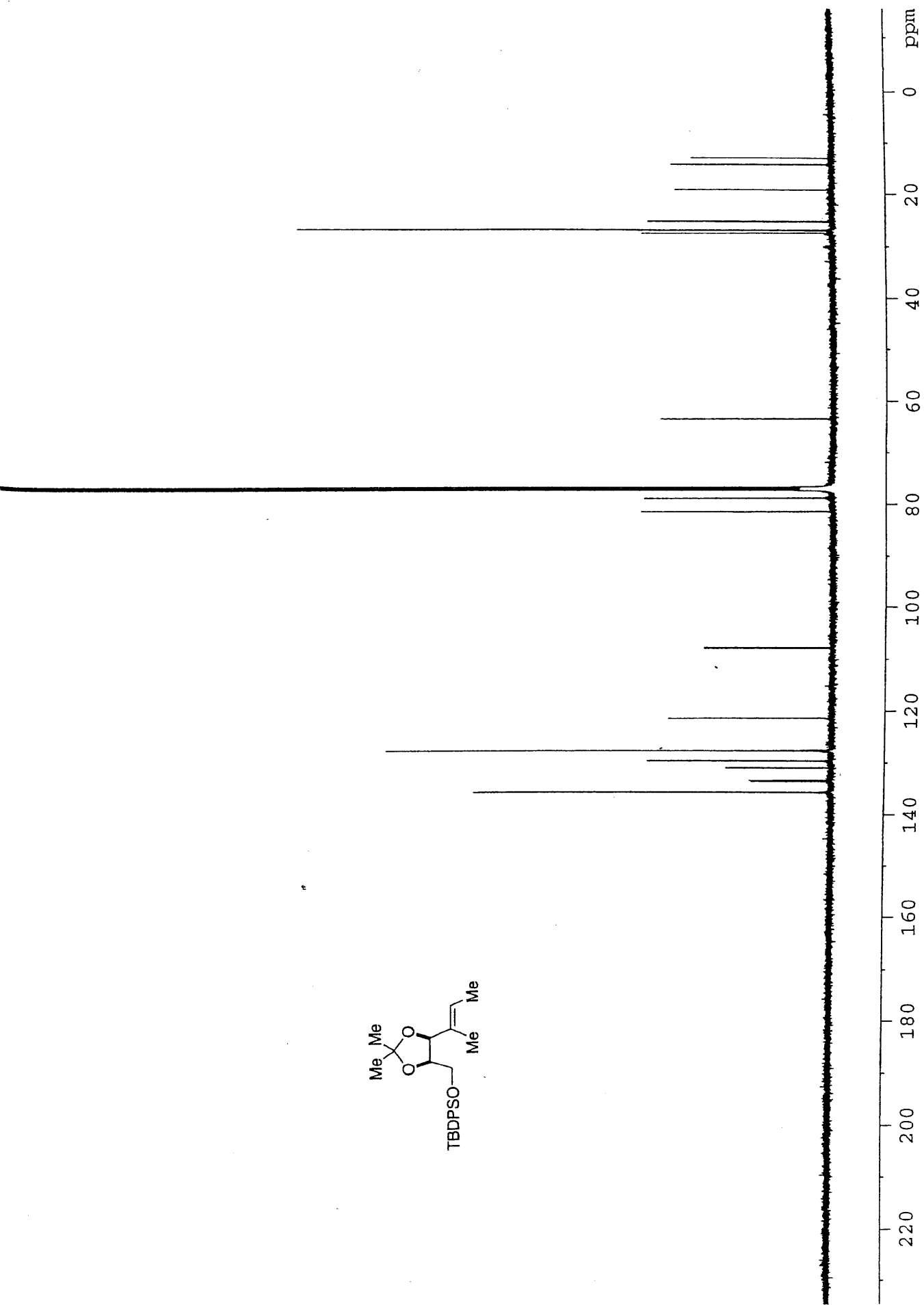
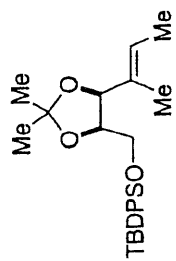


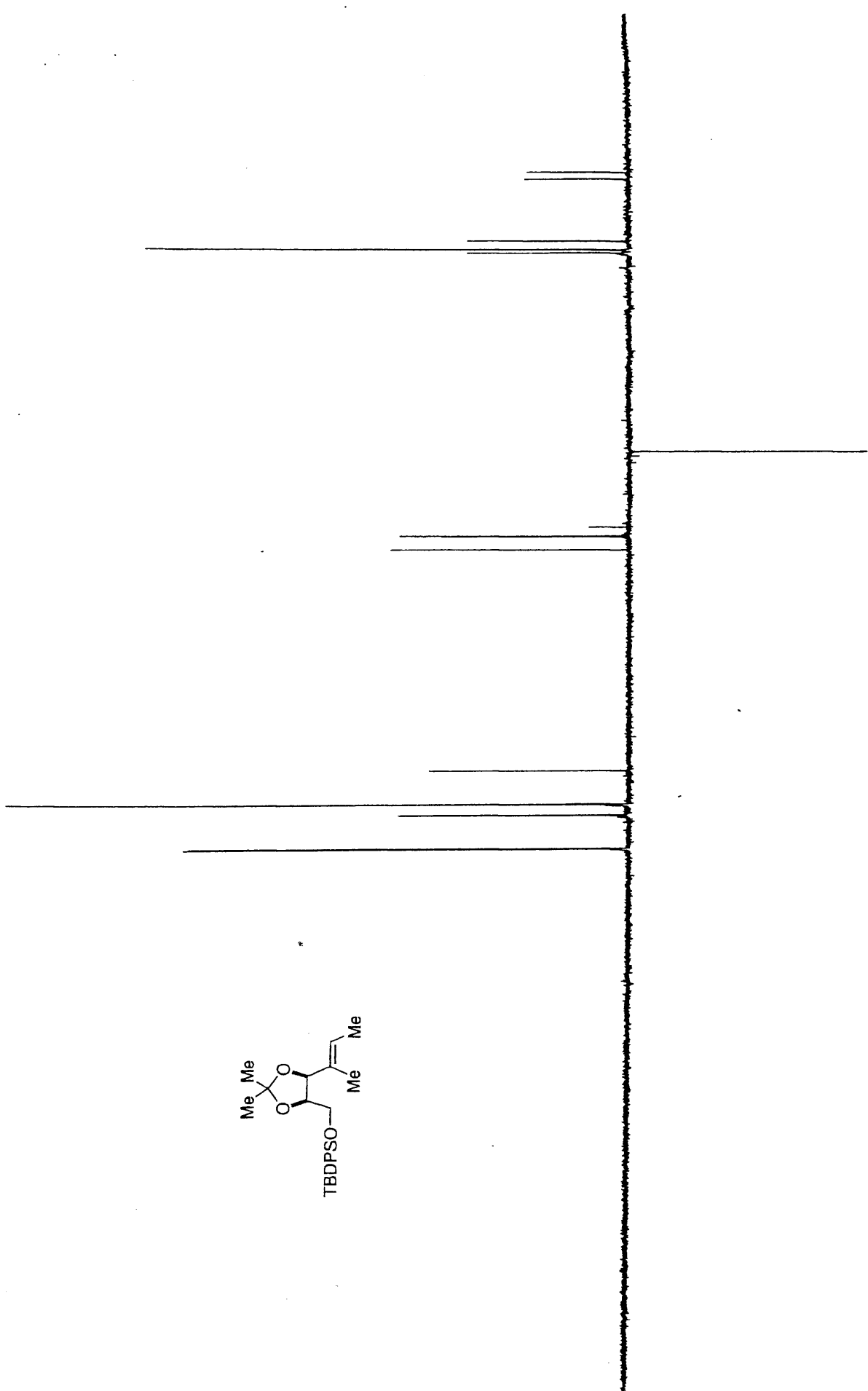
2.82

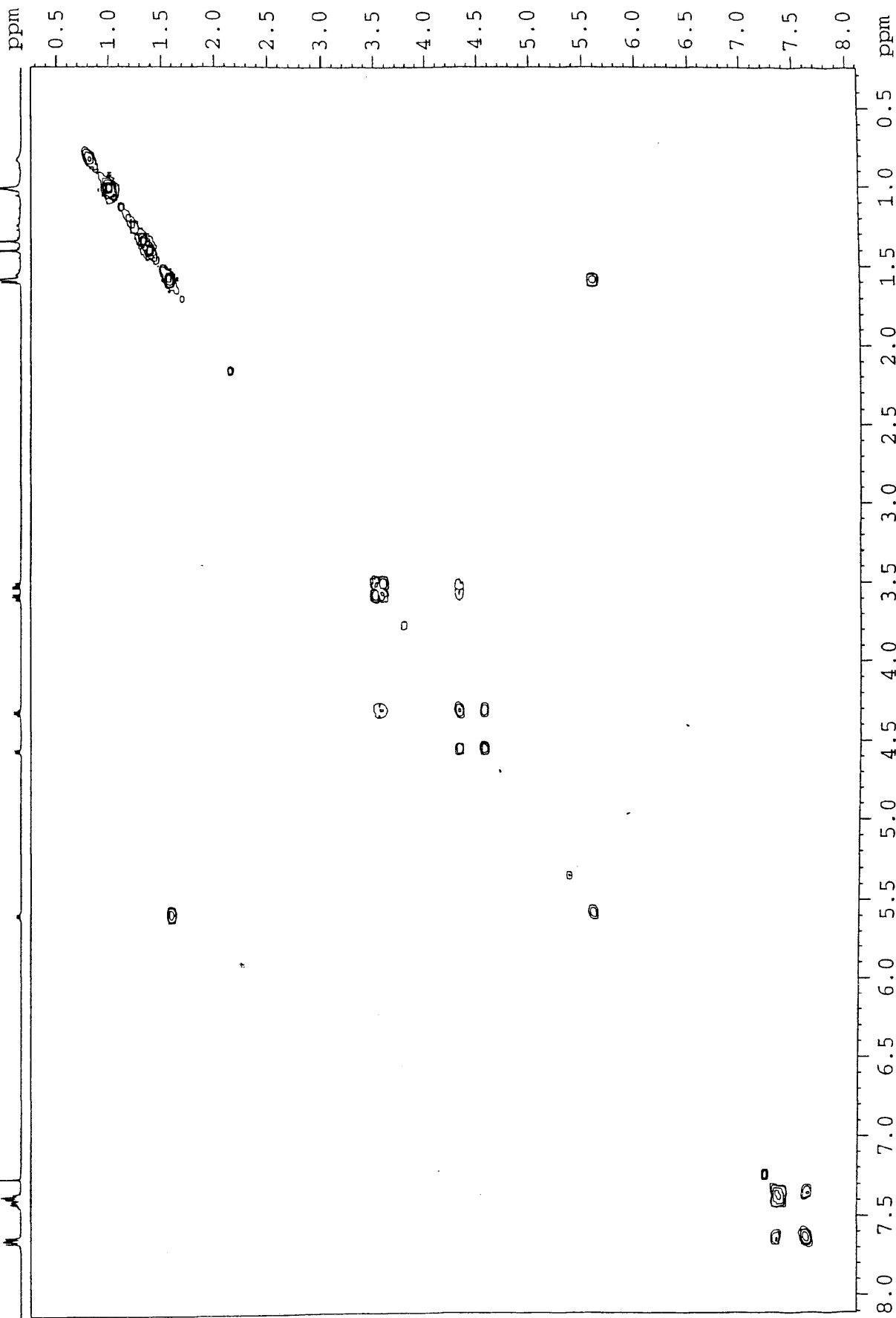


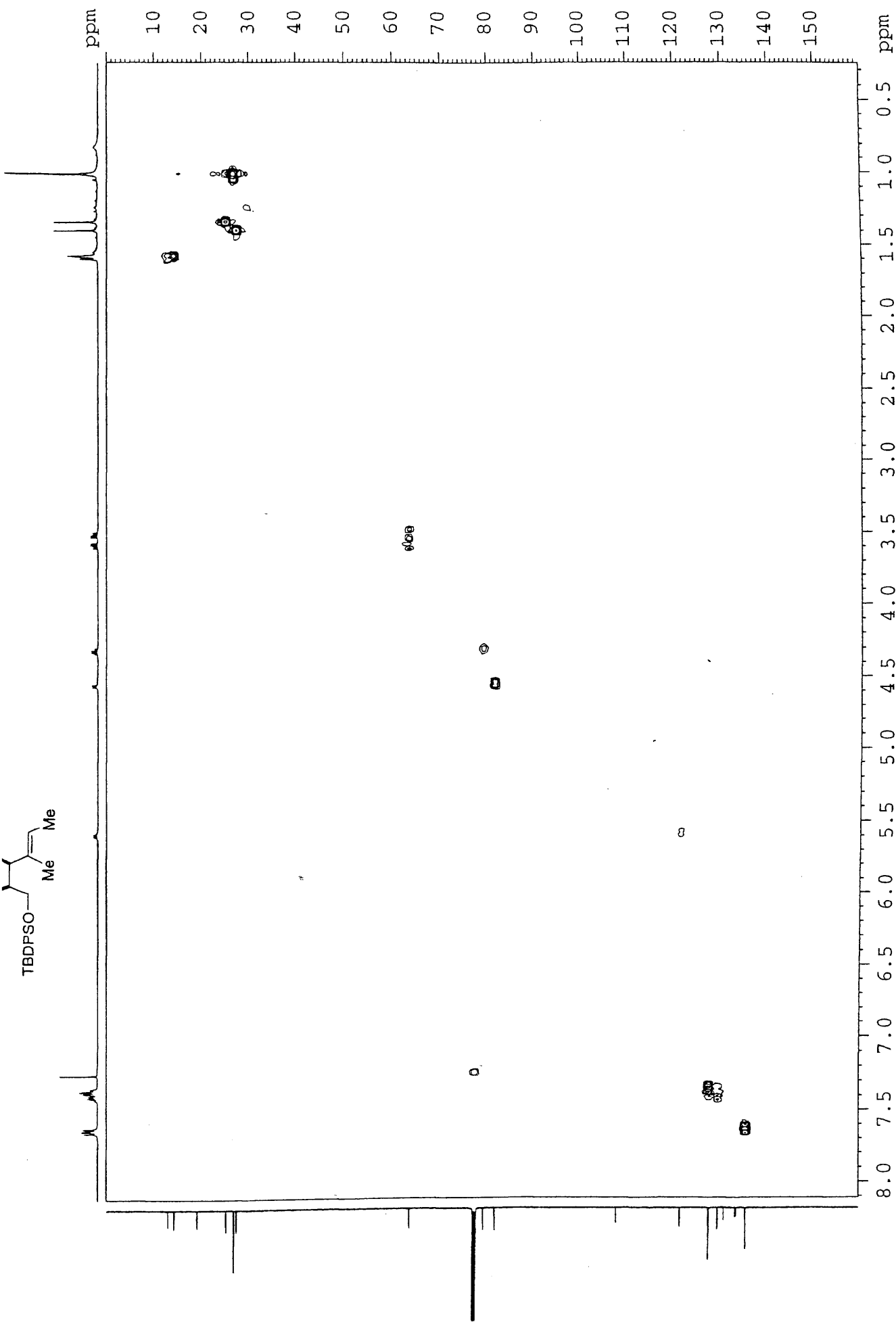


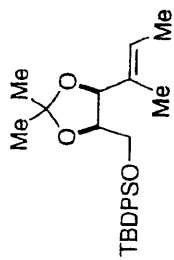
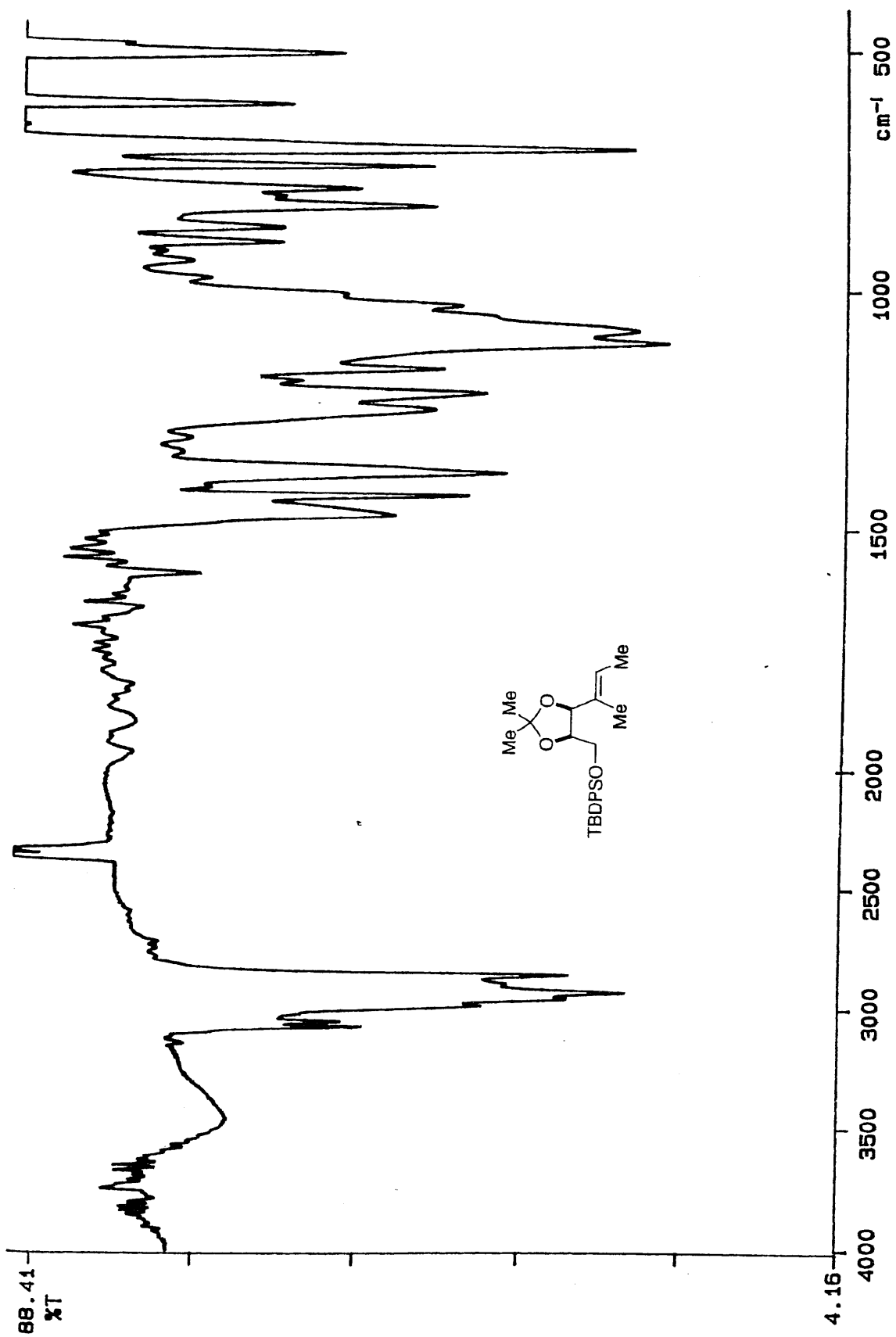




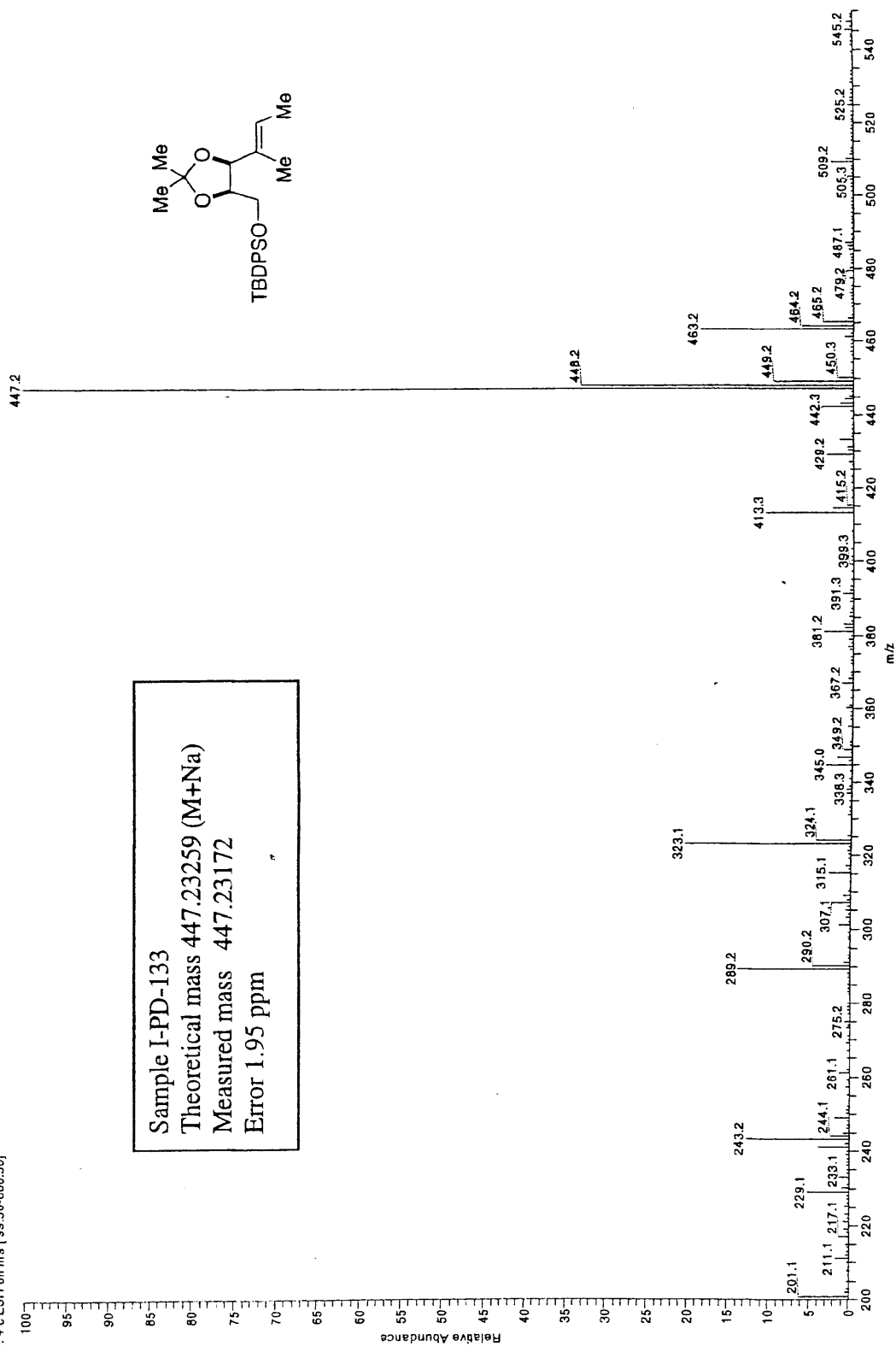
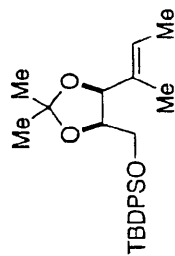




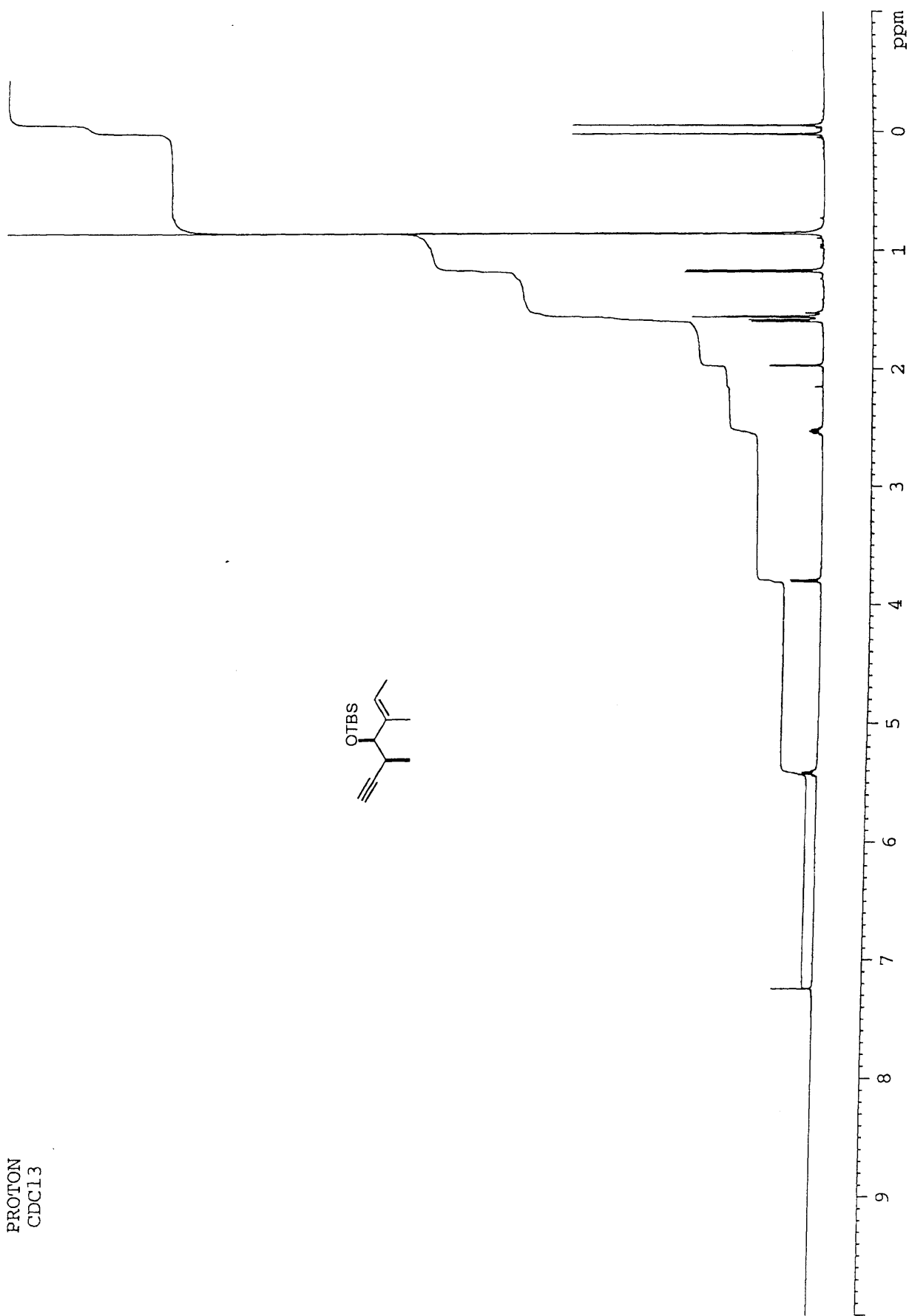
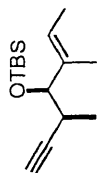




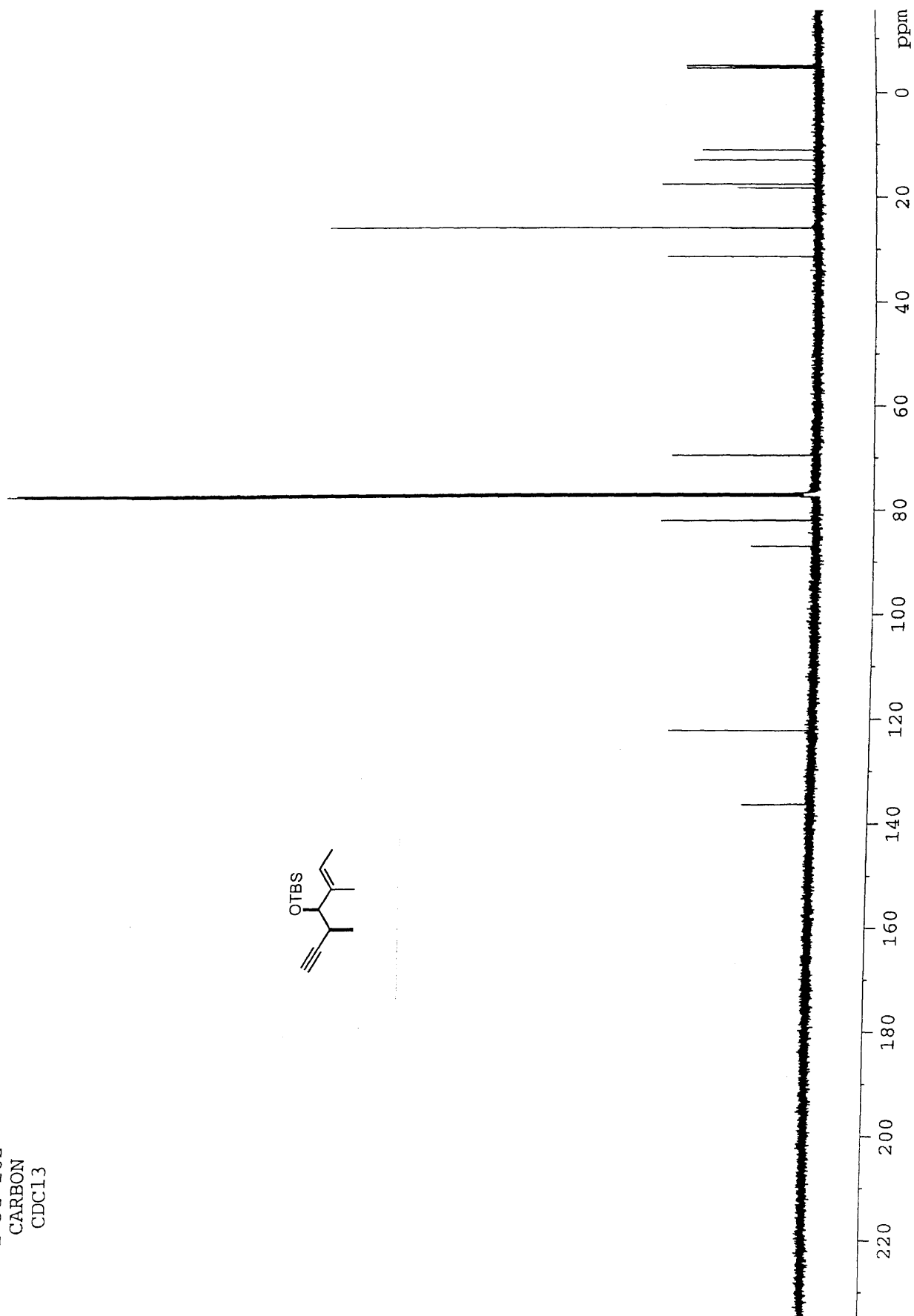
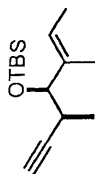
Sample I-PD-133  
Theoretical mass 447.23259 (M+Na)  
Measured mass 447.23172  
Error 1.95 ppm



I-JG-162  
PROTON  
CDCl3

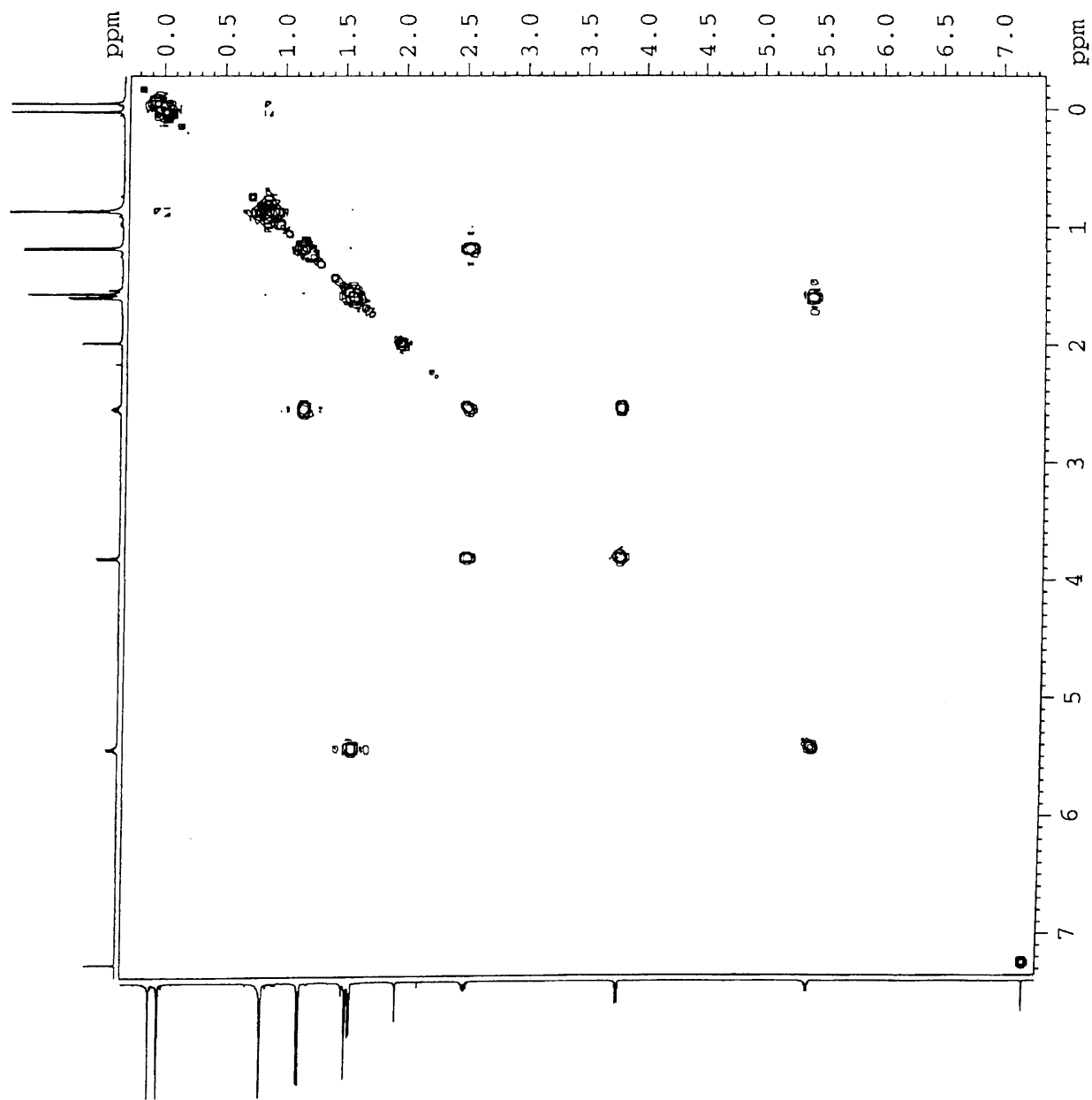
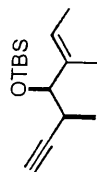


I-JG-162  
CARBON  
CDCl<sub>3</sub>

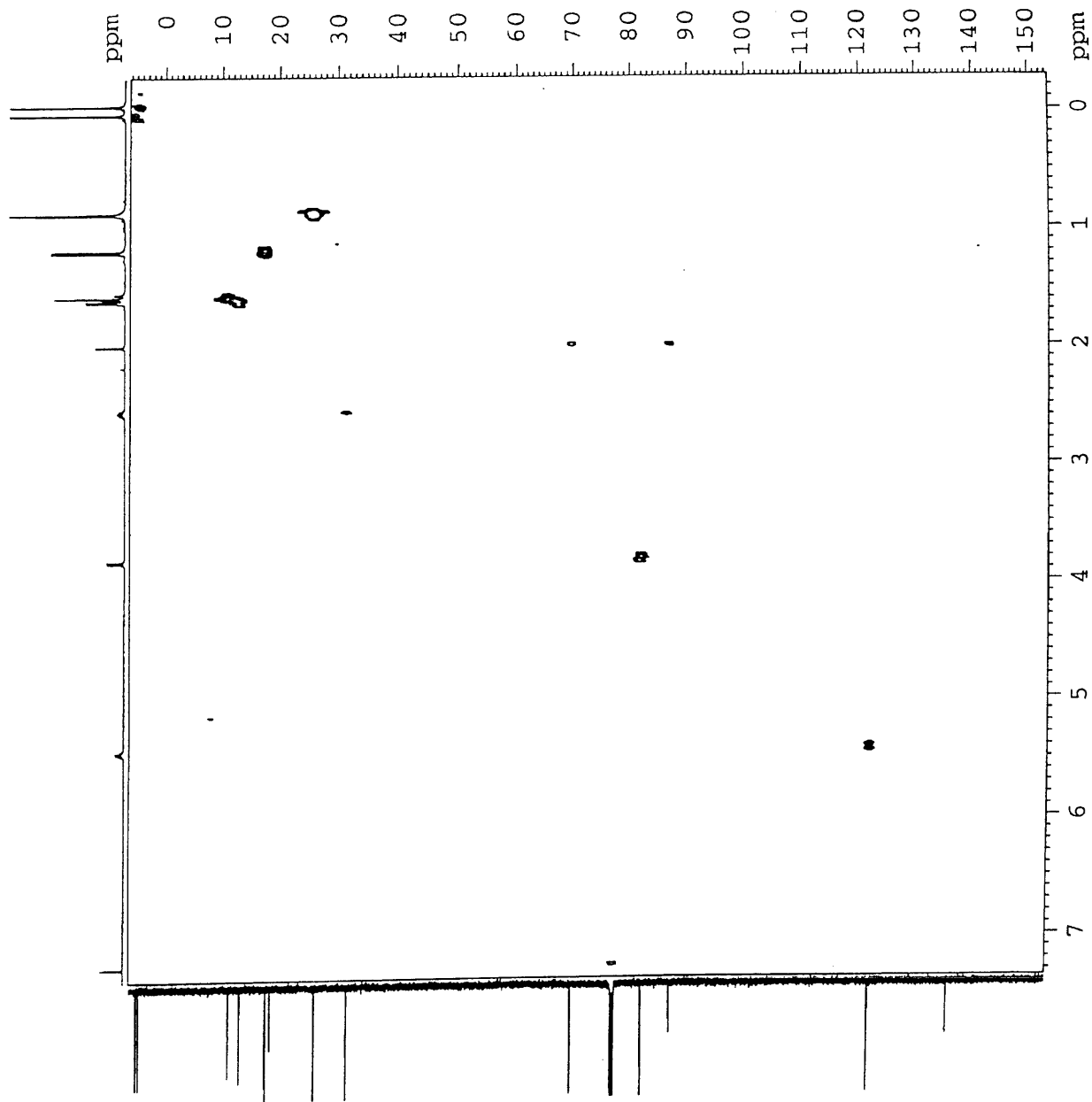
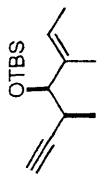


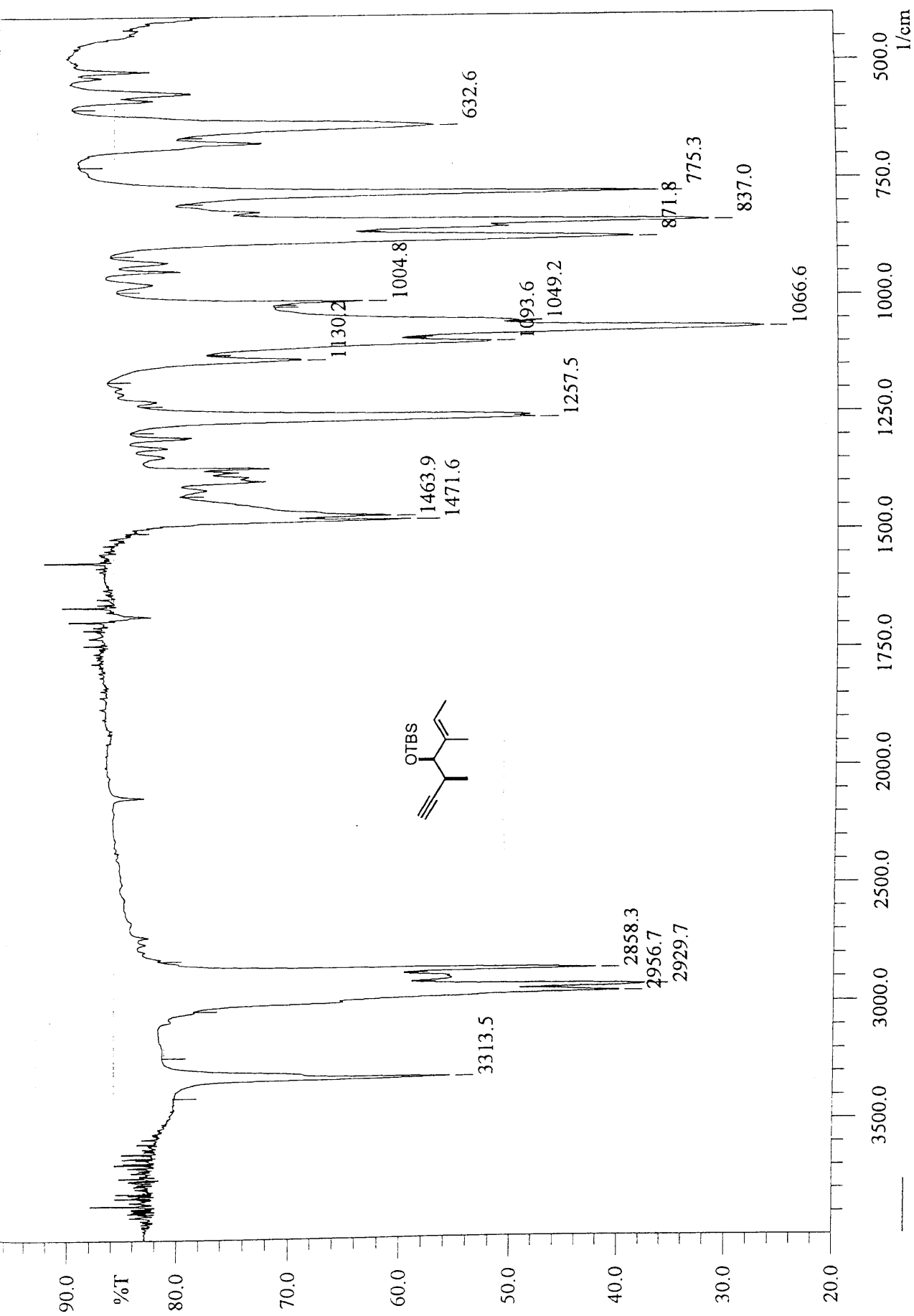


I-JG-162  
COSY  
CDCl<sub>3</sub>

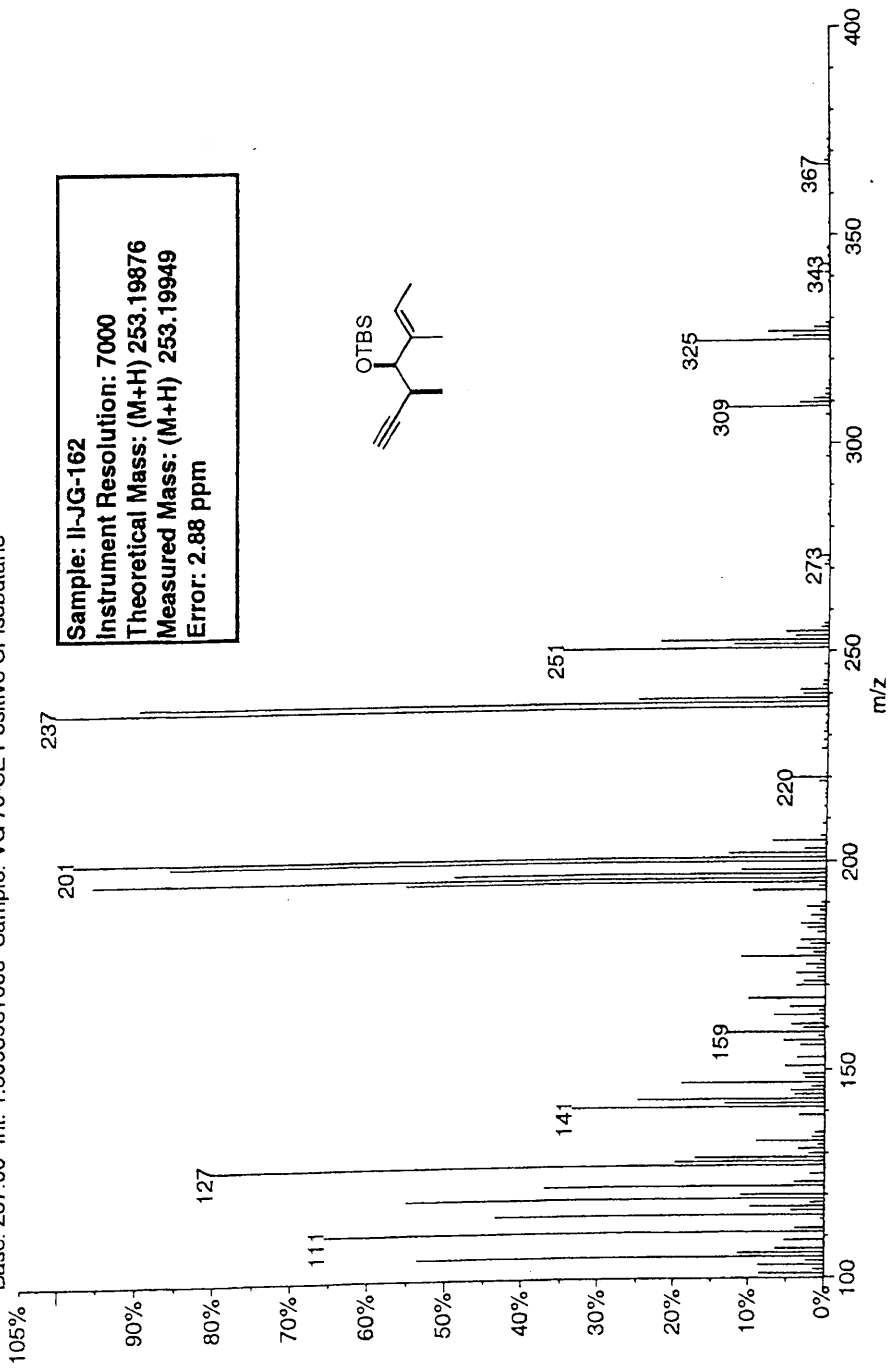


I-JG-162  
HMQC  
CDCl<sub>3</sub>





01101104; Scan Avg 175-181 (40.63 - 42.03 min) - Back  
Base: 237.00 Int: 1.80939e+006 Sample: VG 70-SE Positive Cl-Isobutane

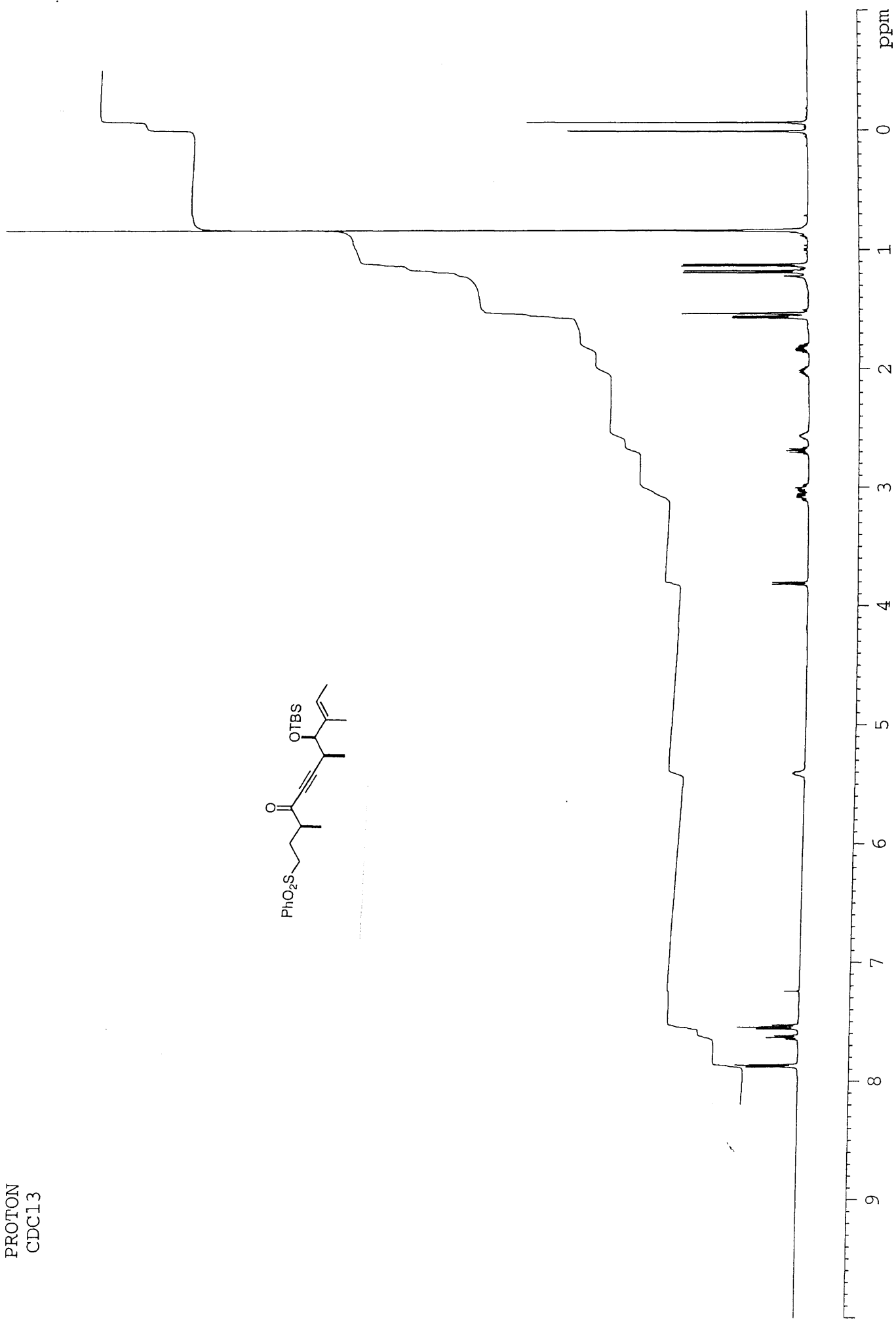
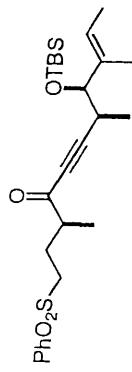


Sample: II-JG-162  
Instrument Resolution: 7000  
Theoretical Mass: (M+H) 253.19876  
Measured Mass: (M+H) 253.19949  
Error: 2.88 ppm

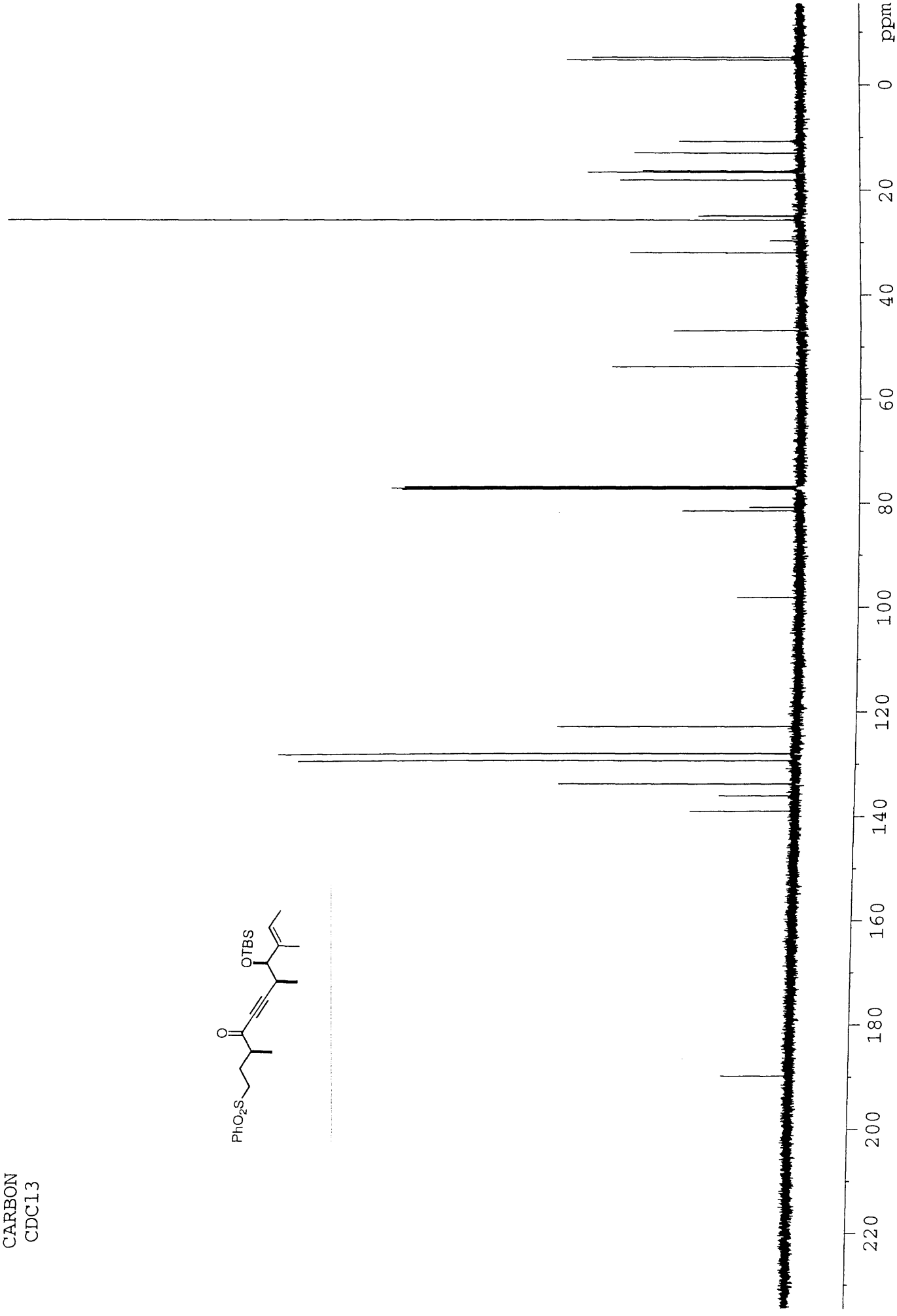
II-JG-116

PROTON

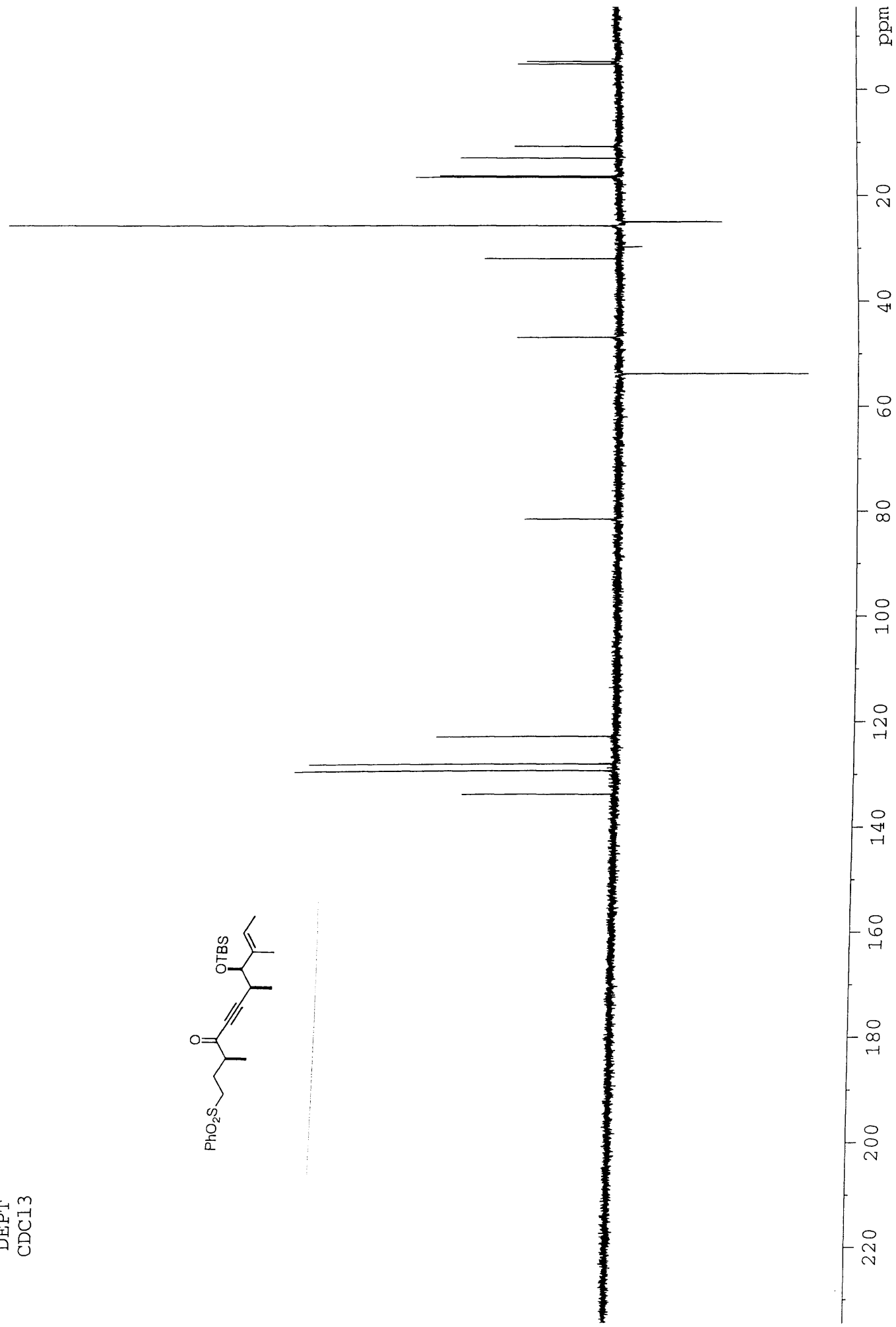
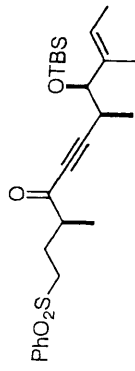
CDC13



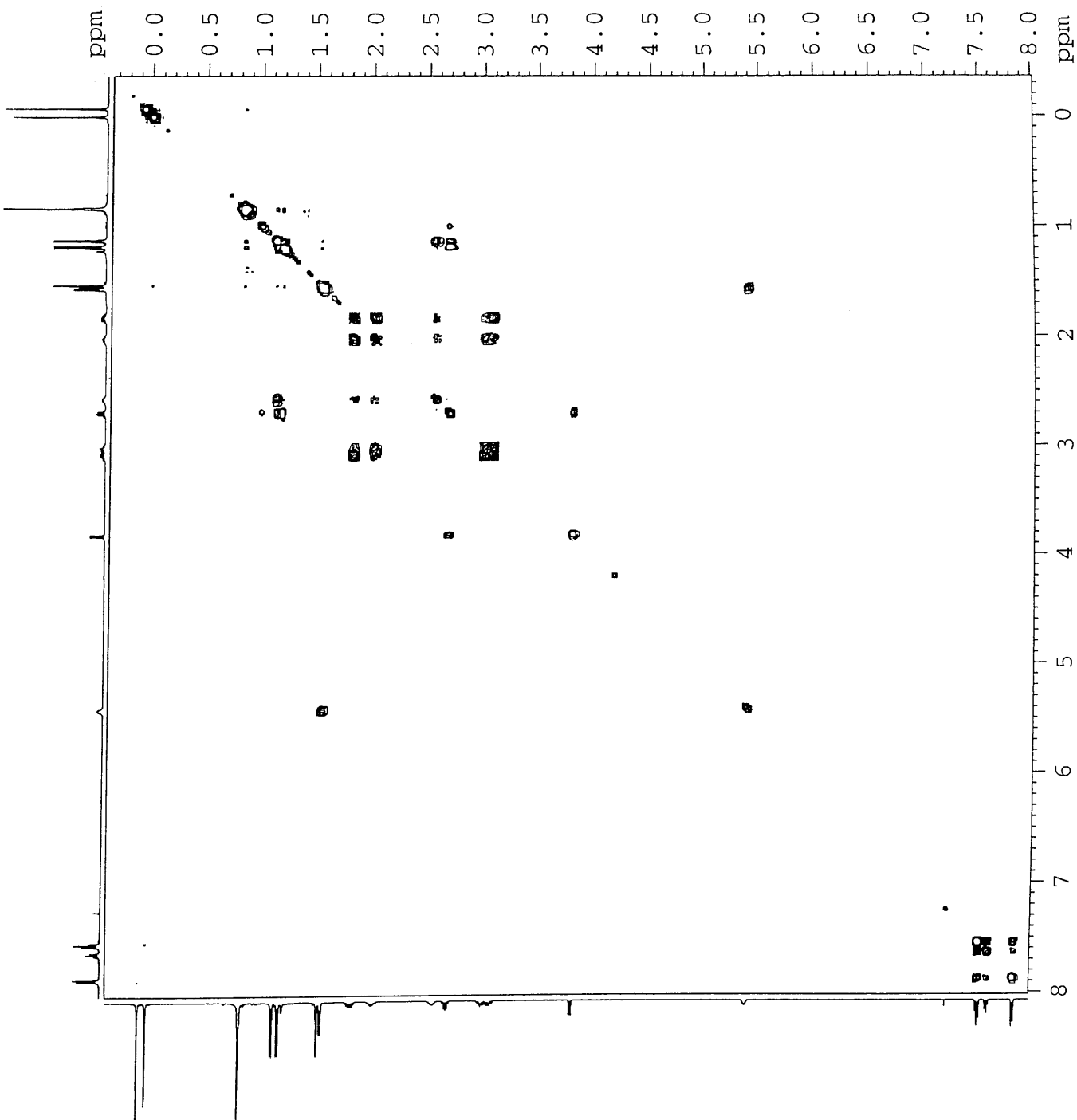
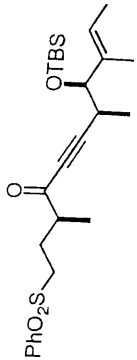
CDC13



II-JG-116  
DEPT  
CDCl<sub>3</sub>

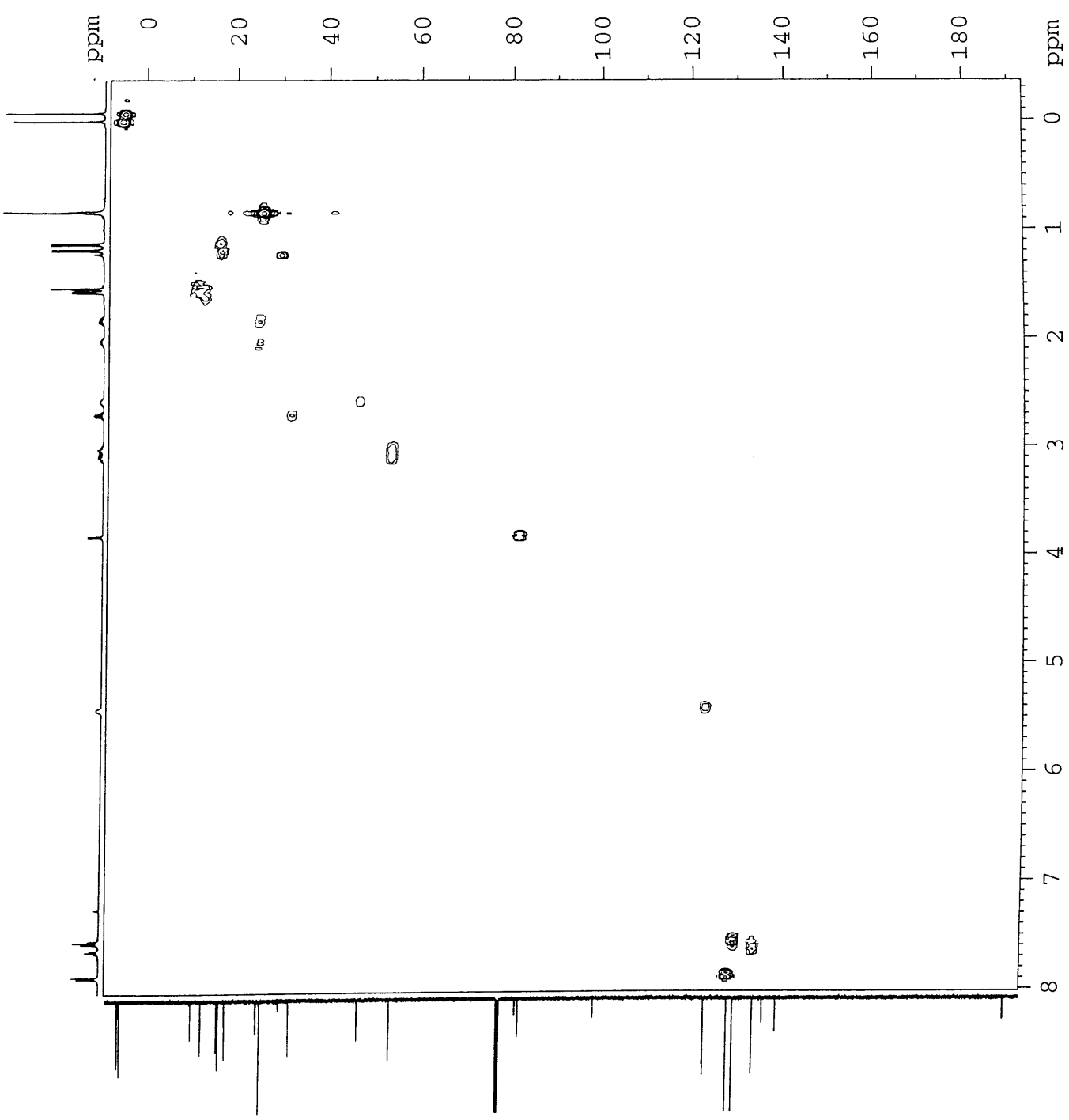
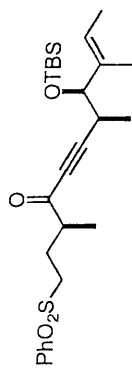


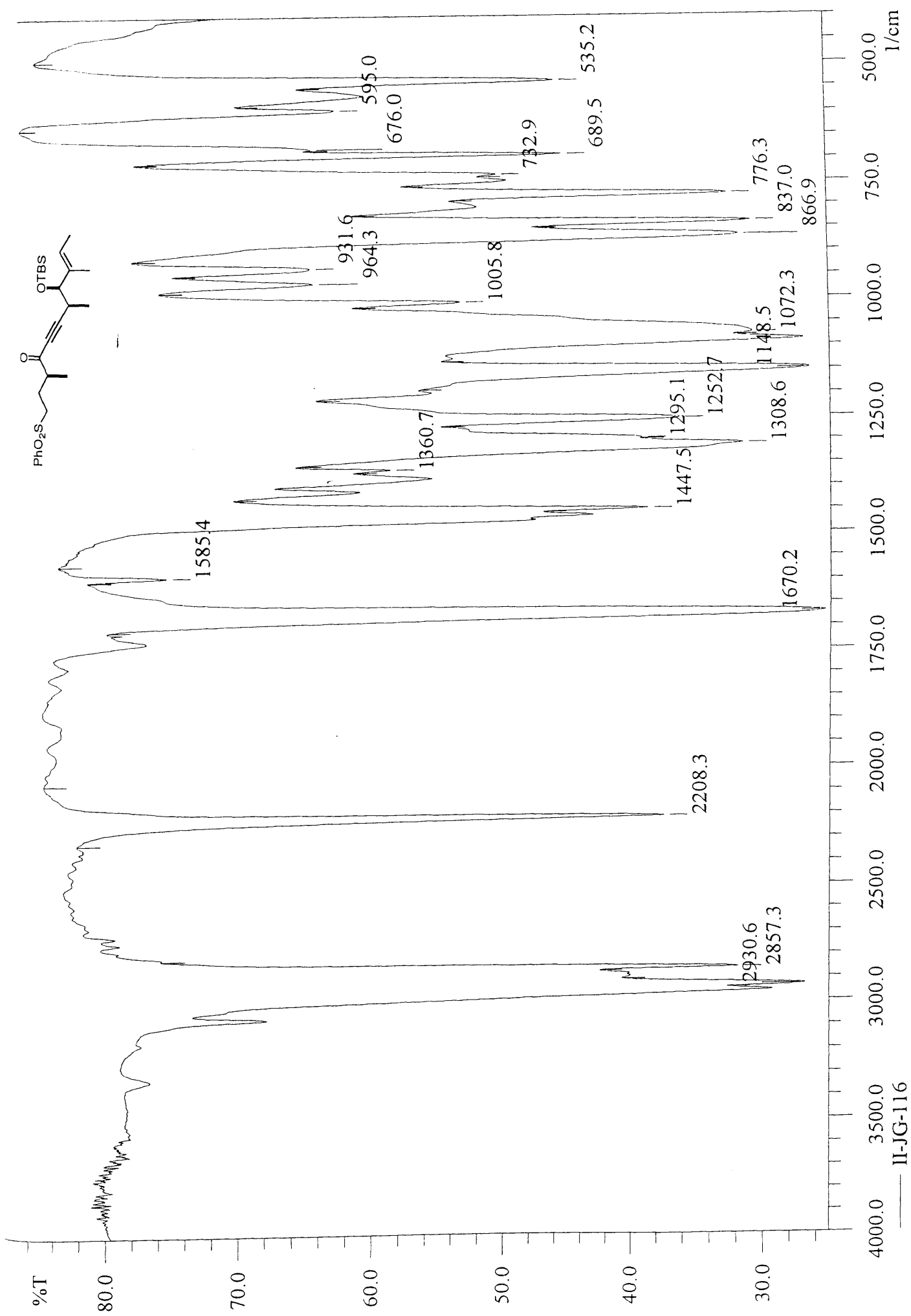
II-JG-116  
COSY  
CDC13





II-JG-116  
HMQC  
CDC13

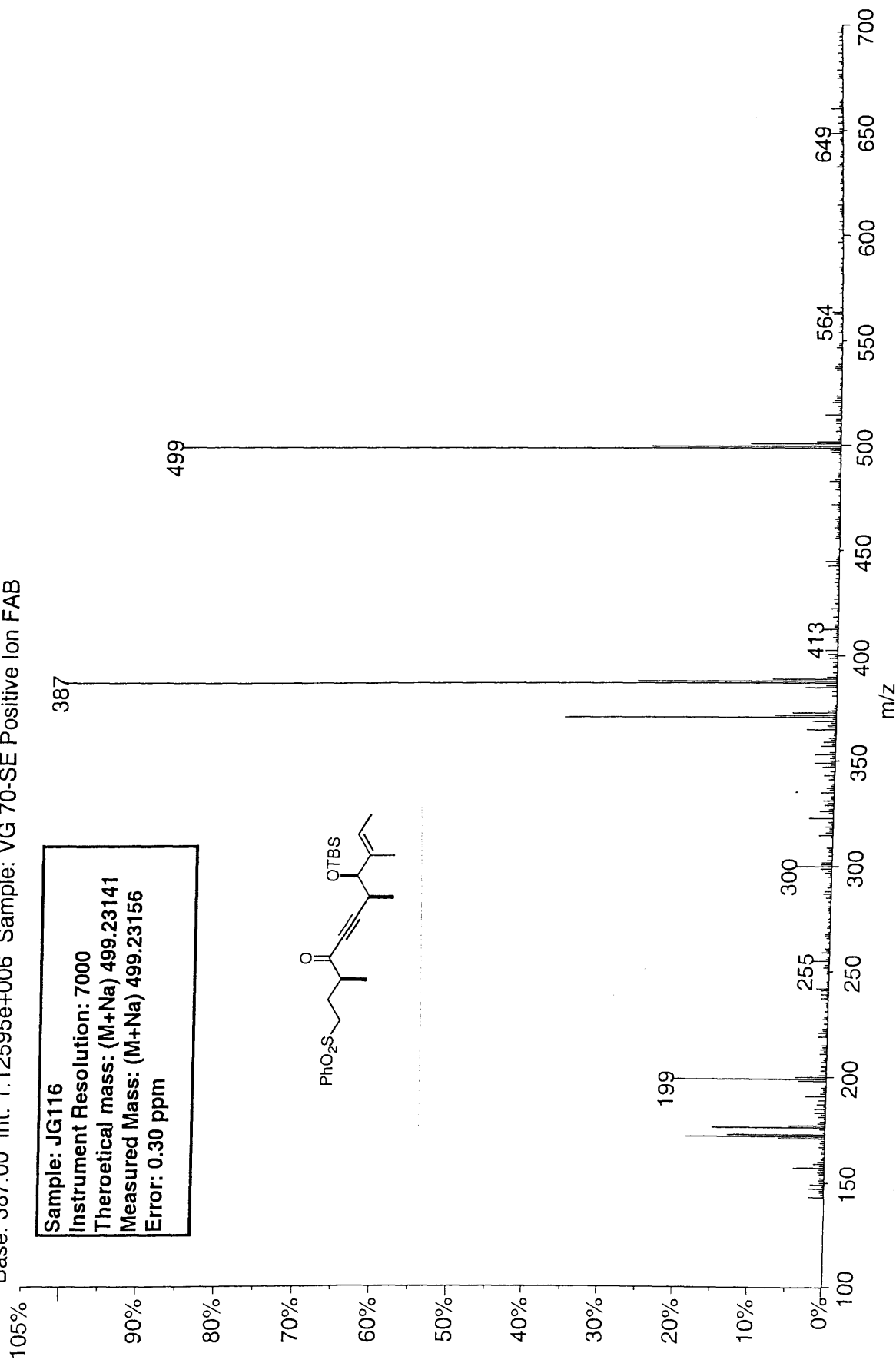
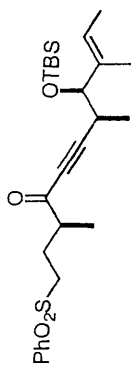




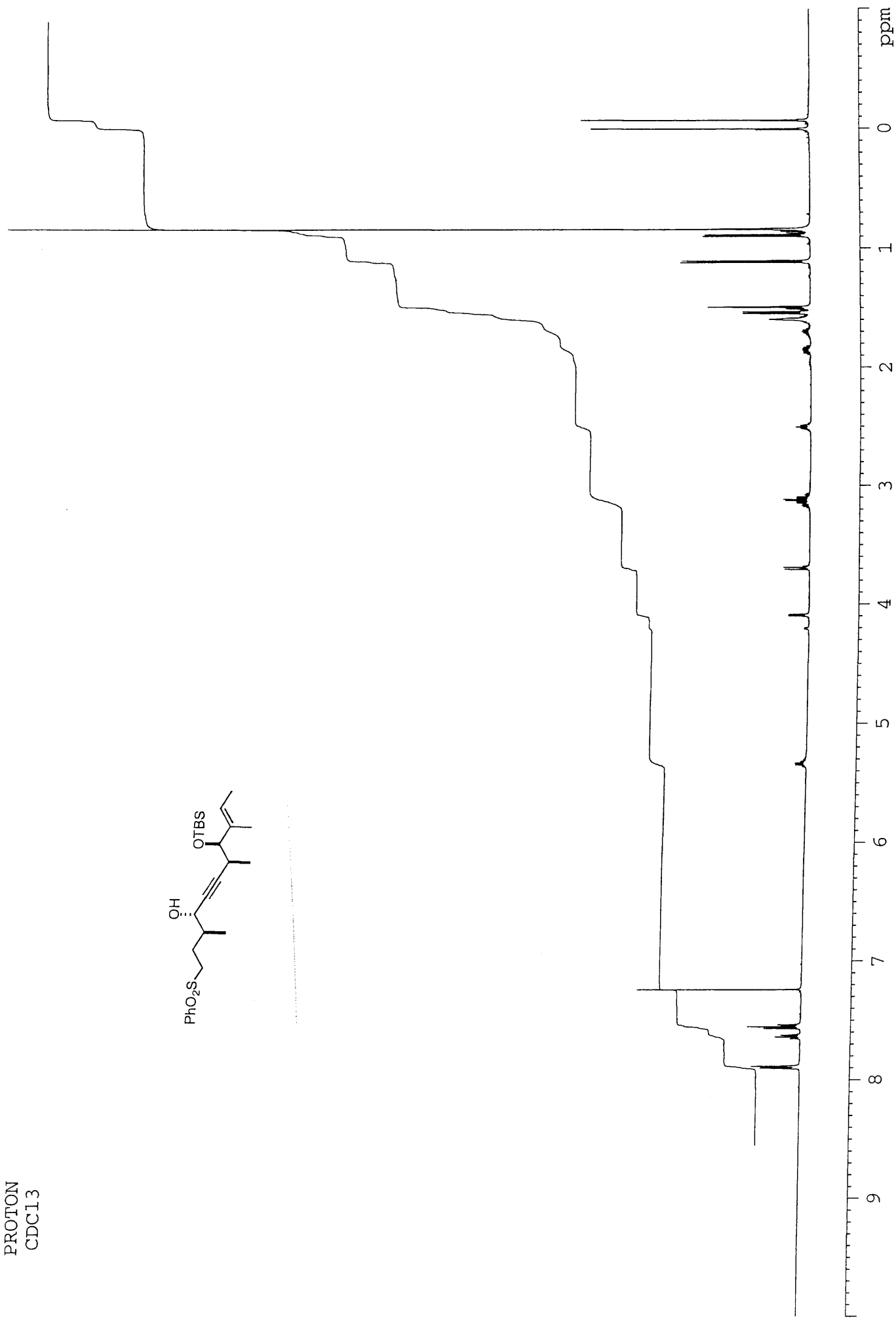
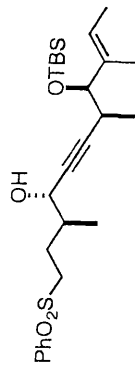
II-JG-116

01300306: Scan 231 (42.30 min) - Back  
Base: 387.00 Int: 1.12595e+006 Sample: VG 70-SE Positive Ion FAB

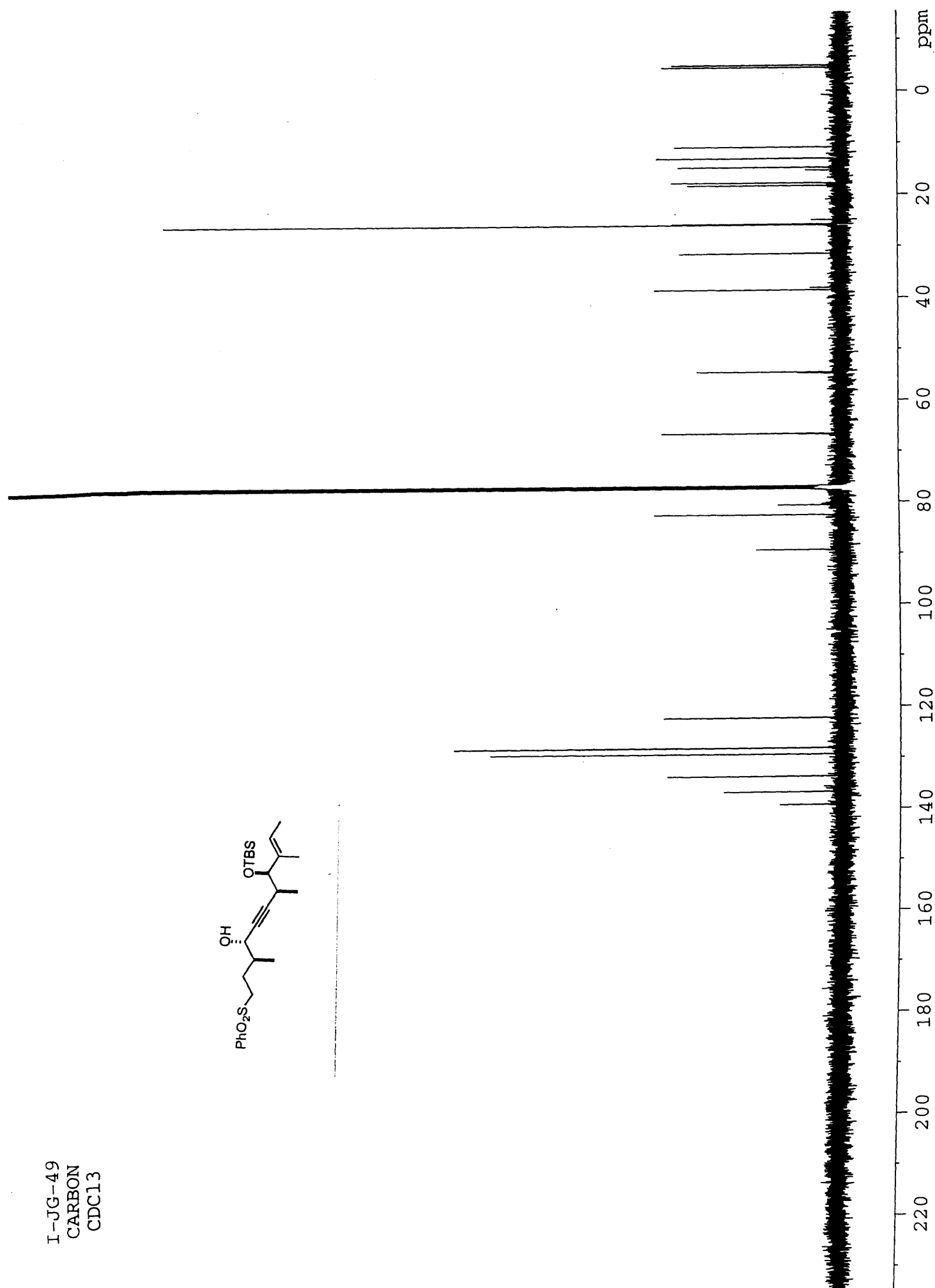
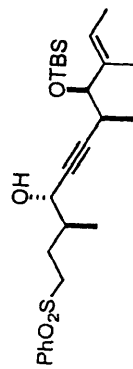
Sample: JG116  
Instrument Resolution: 7000  
Theoretical mass: (M+Na) 499.23141  
Measured Mass: (M+Na) 499.23156  
Error: 0.30 ppm



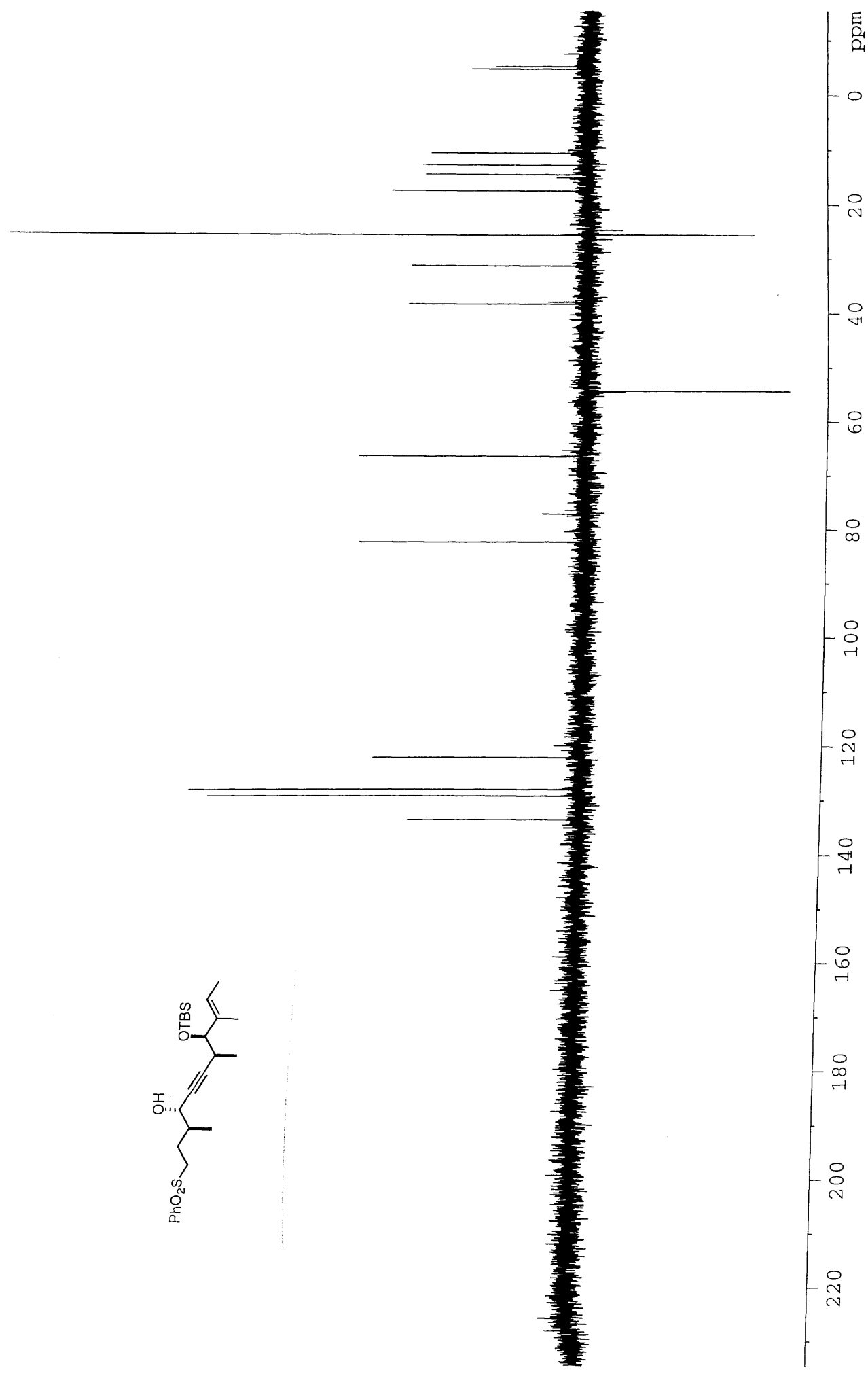
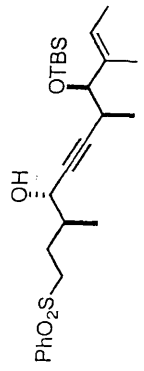
I-JG-149  
PROTON  
CDCl3



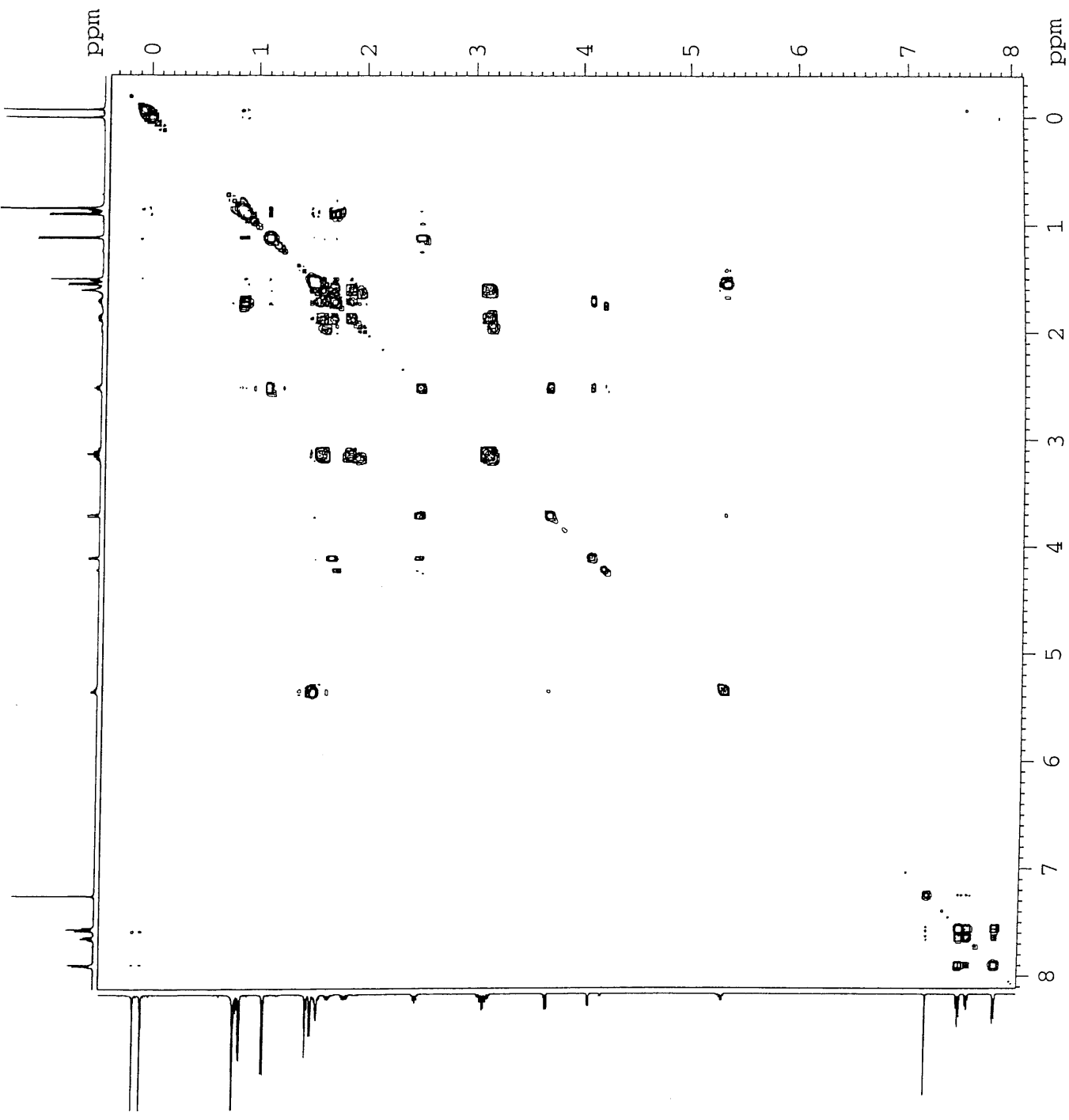
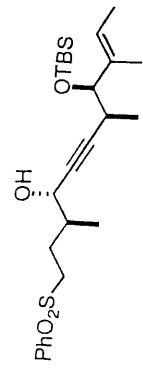
I-JG-49  
CARBON  
CDC13



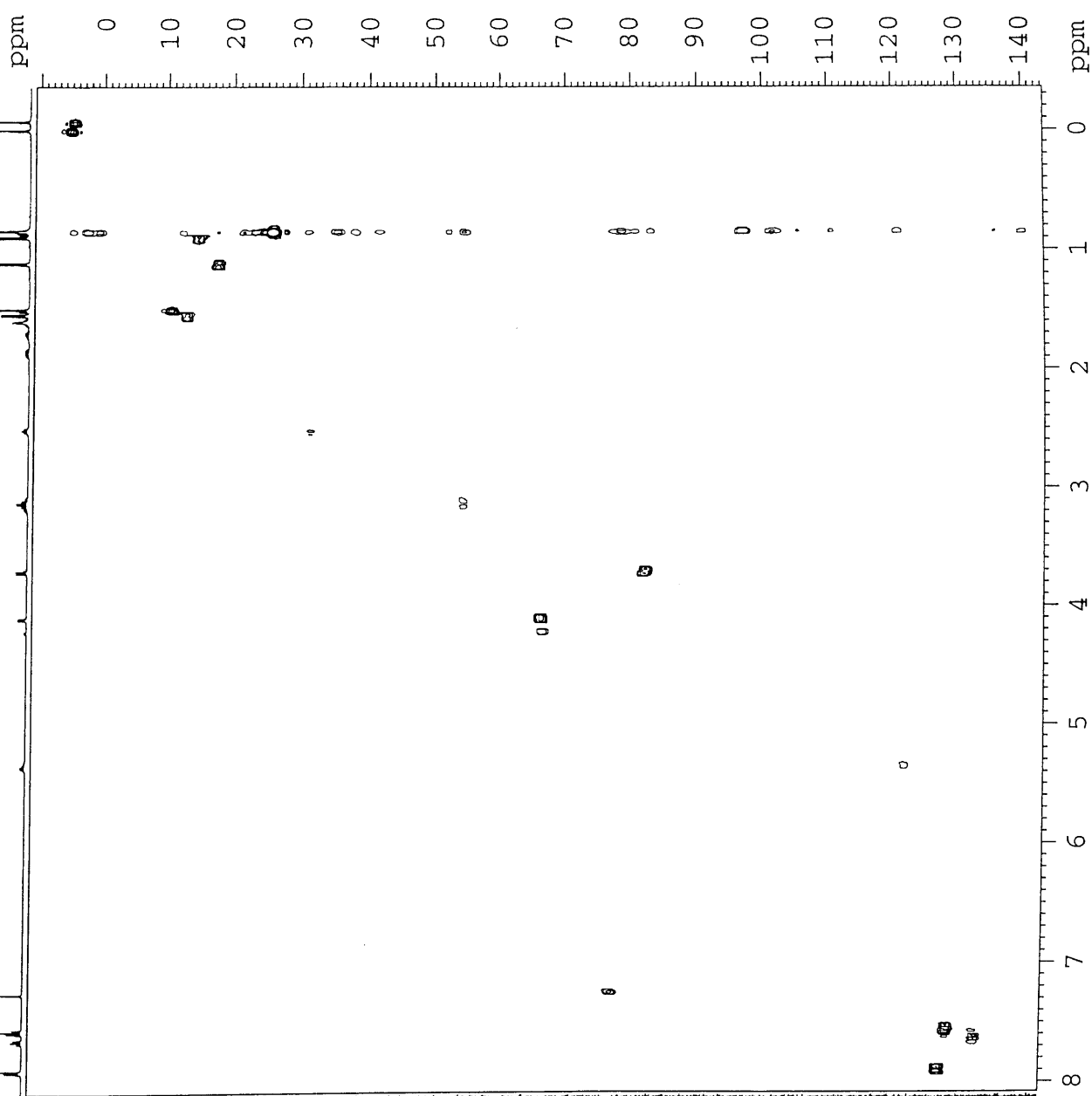
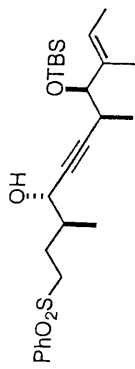
[<sup>13</sup>C]-JG-14c  
DEPT  
CDCl<sub>3</sub>



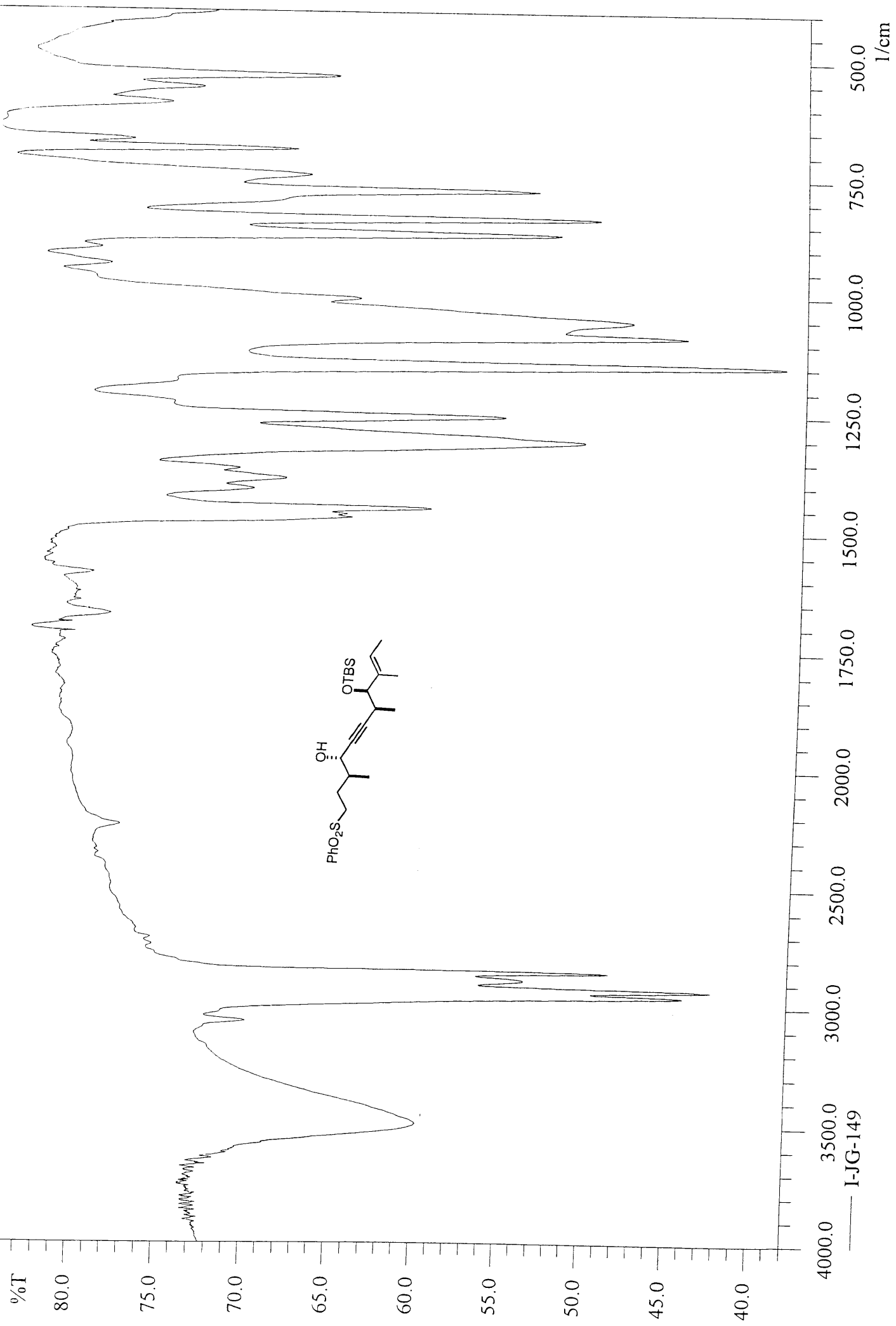
I-JG-49  
COSY  
CDCl3



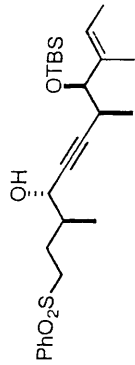
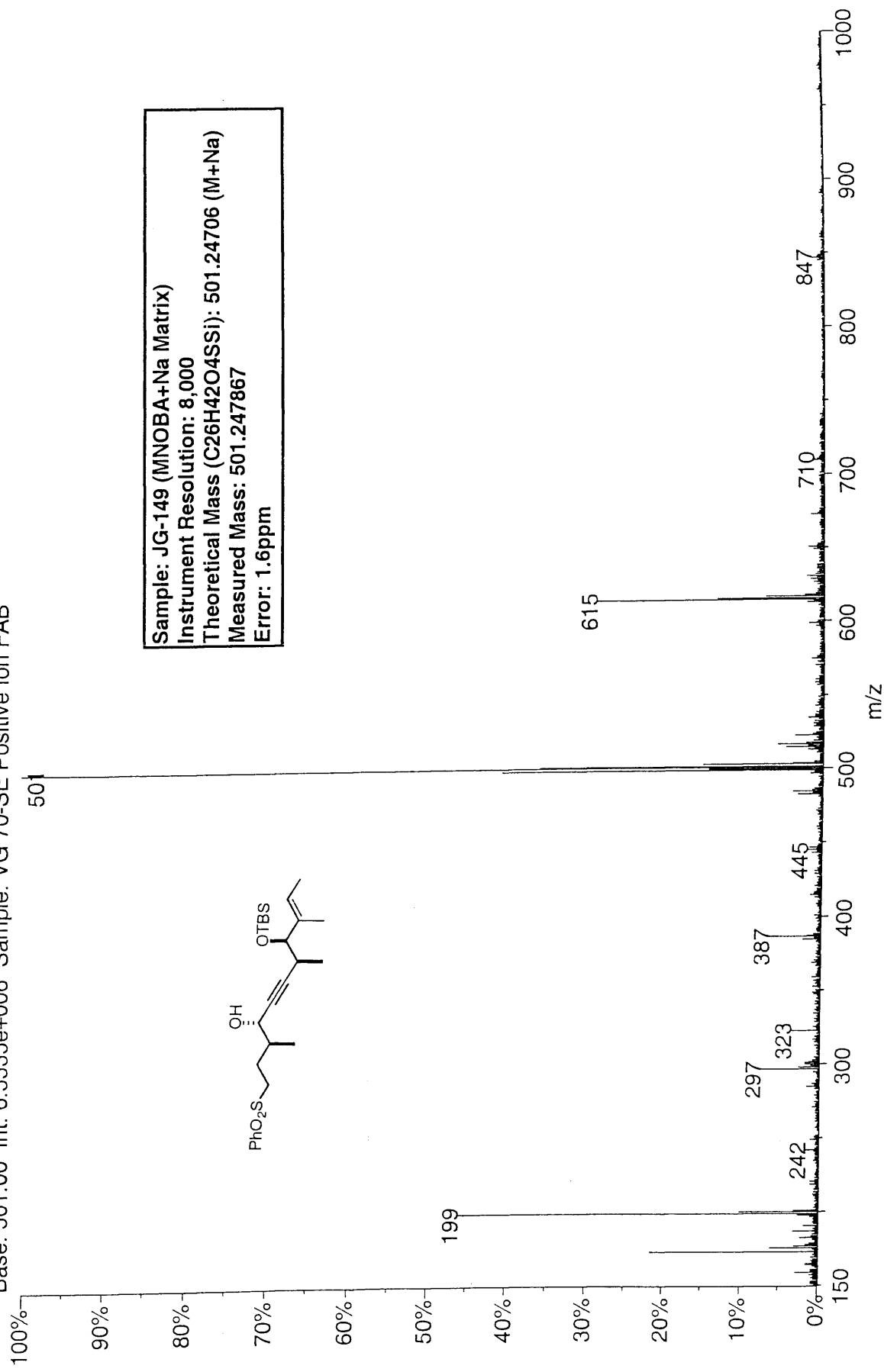
I-JG-149  
HMQC  
CDCl<sub>3</sub>





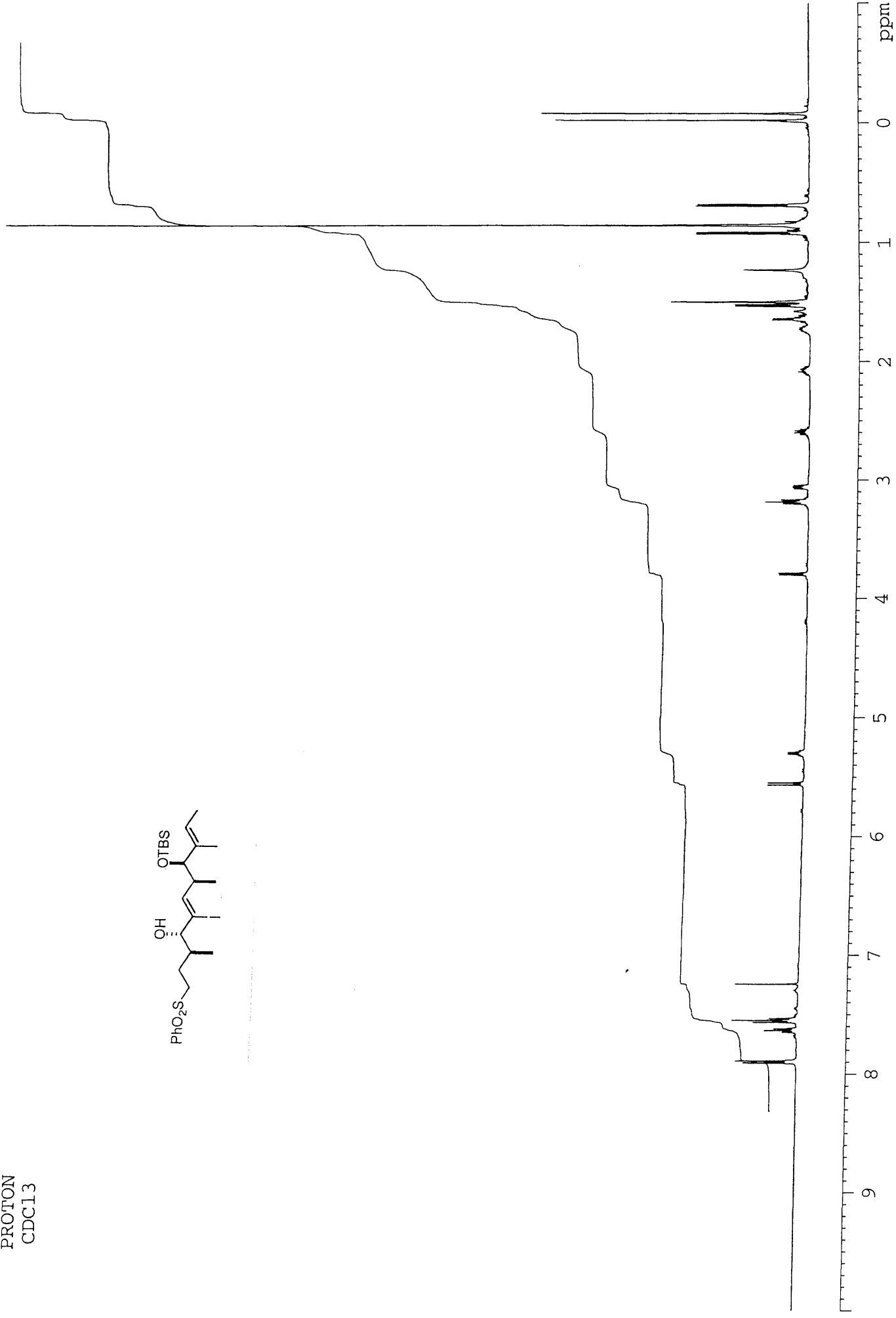
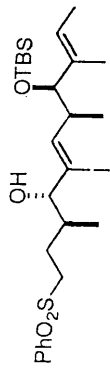


Base: 501.00 Int: 6.5535e+006 Sample: VG 70-SE Positive Ion FAB

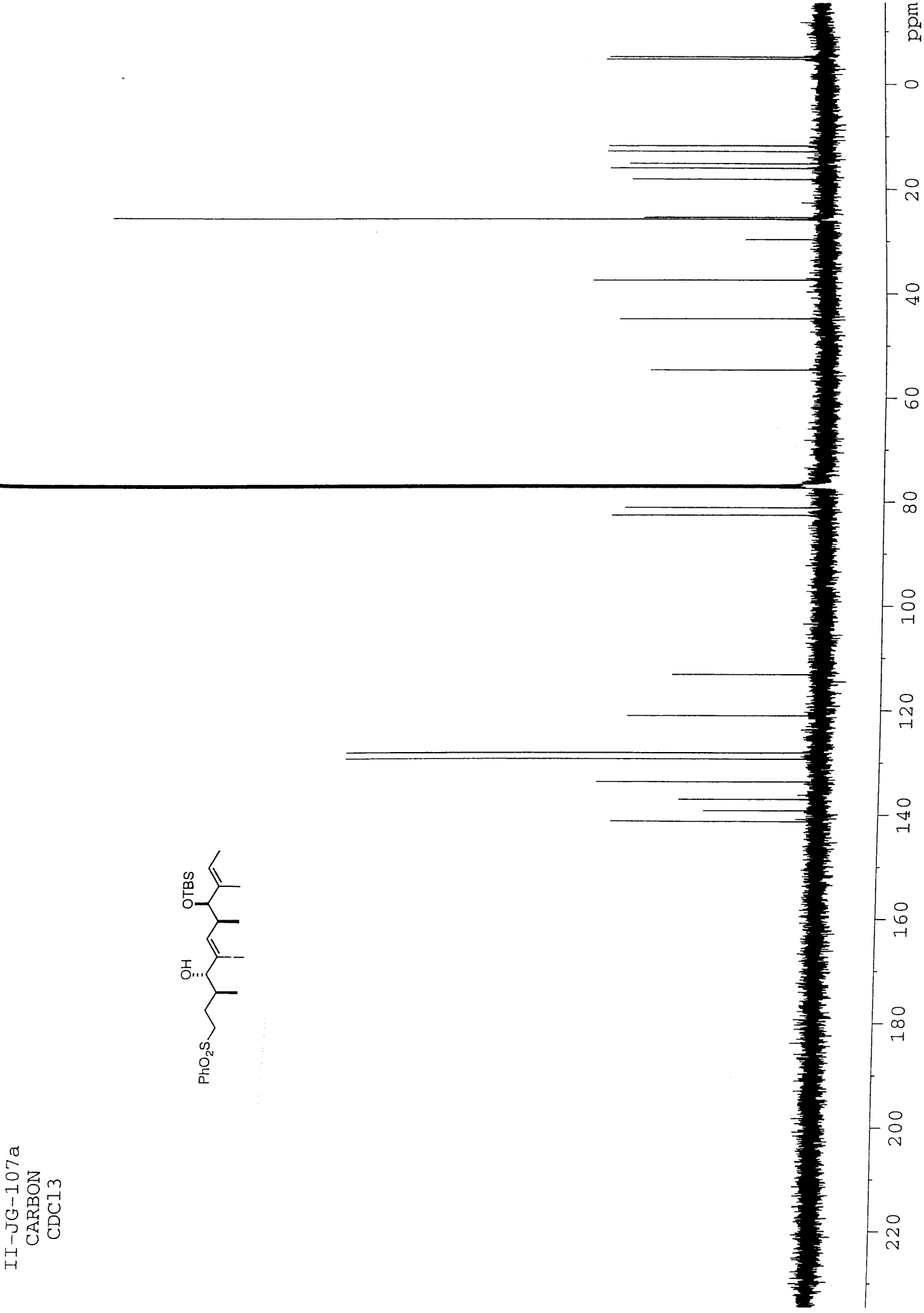
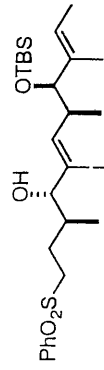


Sample: JG-149 (MNOBA+Na Matrix)  
Instrument Resolution: 8,000  
Theoretical Mass (C26H42O4SSI): 501.24706 (M+Na)  
Measured Mass: 501.247867  
Error: 1.6ppm

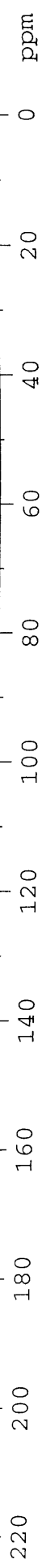
II-JG-107a  
PROTON  
CDCl3



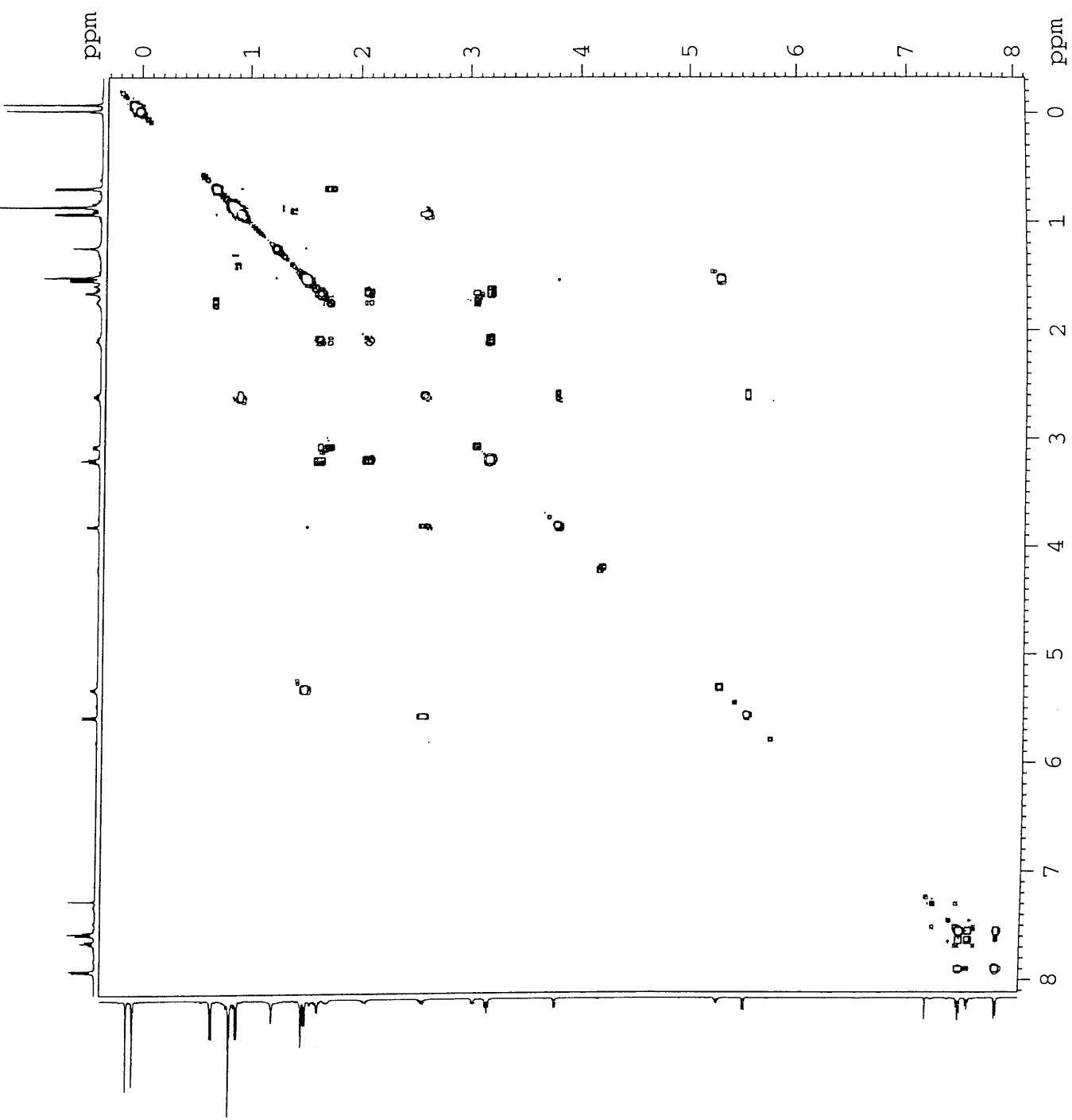
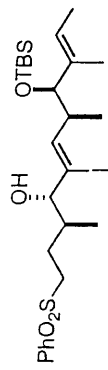
II-JG-107a  
CARBON  
CDC13



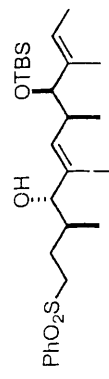
CDC13

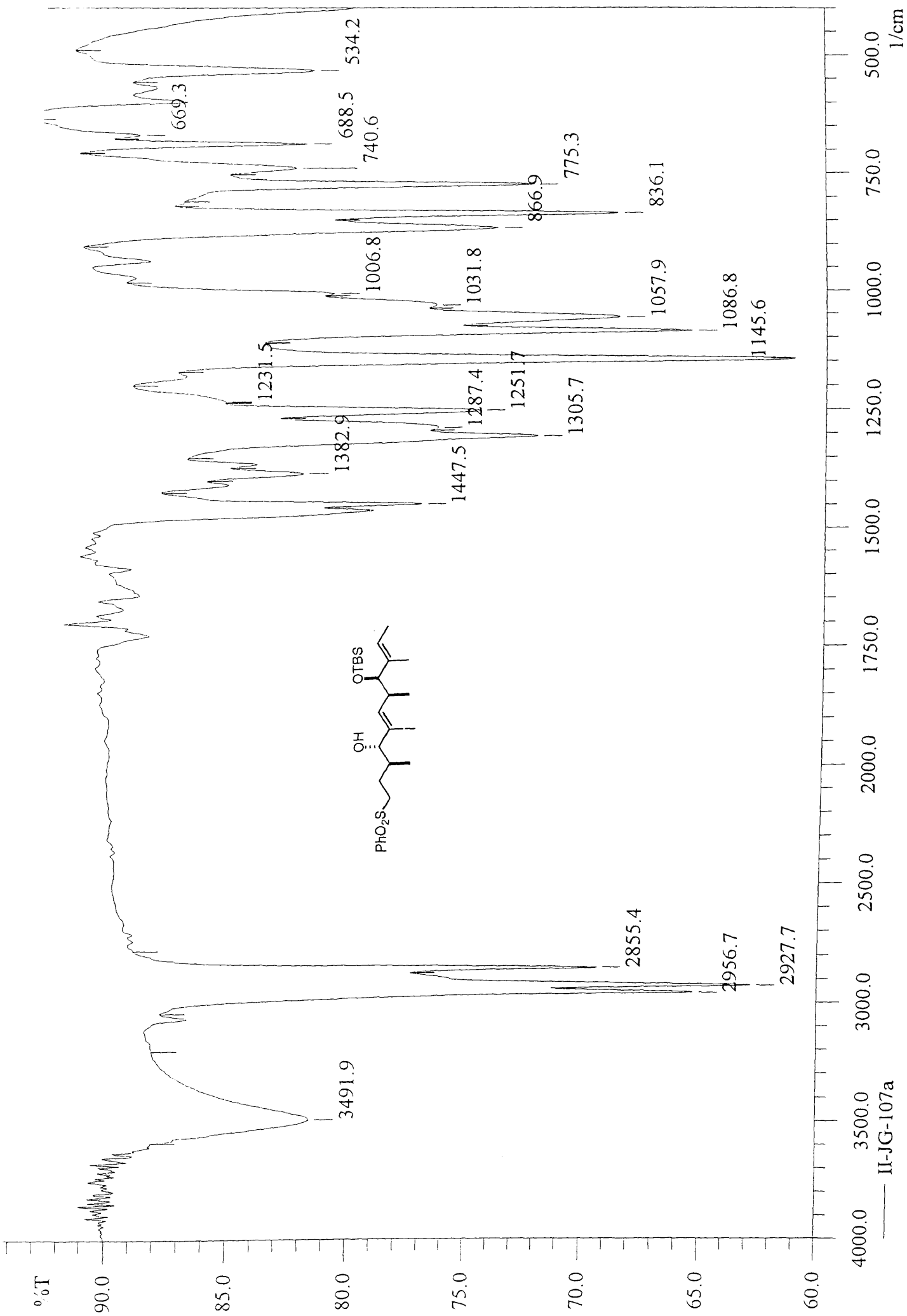


II-JG-107a  
COSY  
CDC13



2D NMR spectrum of compound 1. The x-axis is labeled  $^1\text{H}$  and the y-axis is labeled  $^{13}\text{C}$ . The spectrum shows correlations between protons and carbons, with a large cross-peak at approximately (1.0 ppm, 125 ppm) and another at (4.0 ppm, 80 ppm).

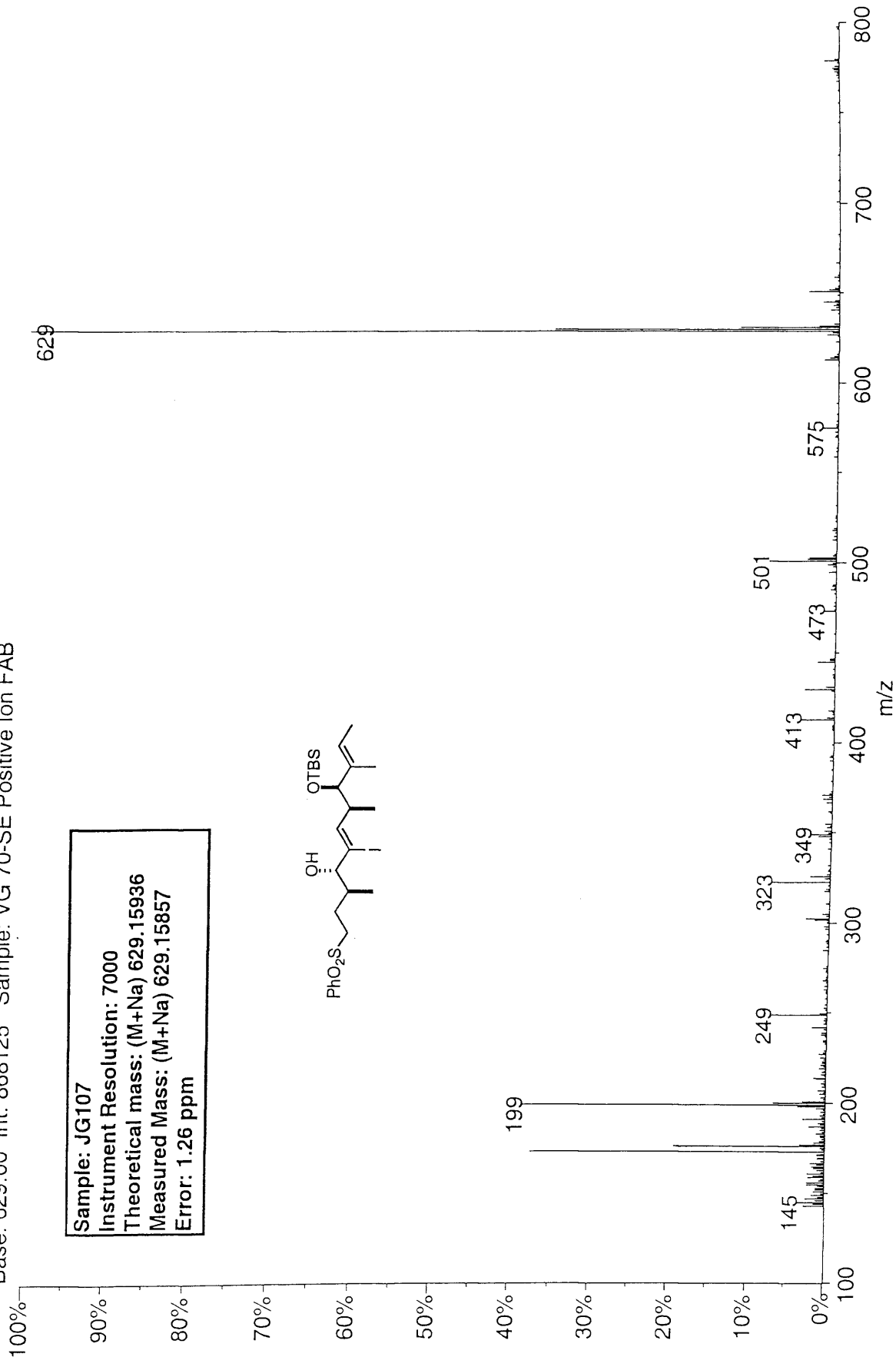
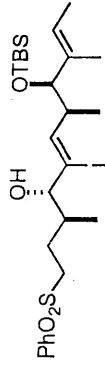




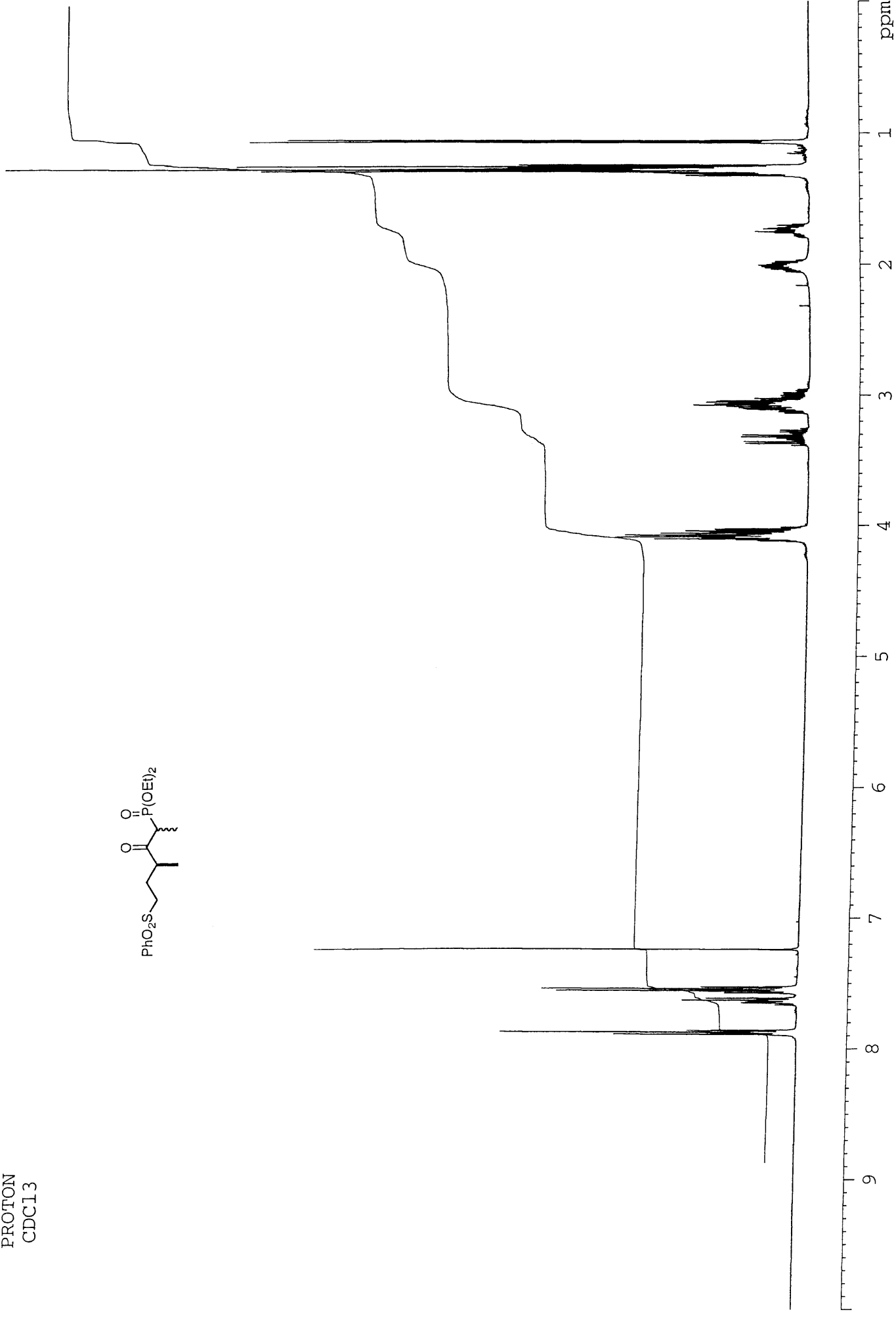
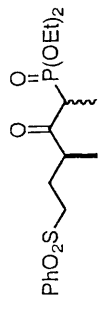


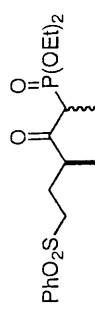
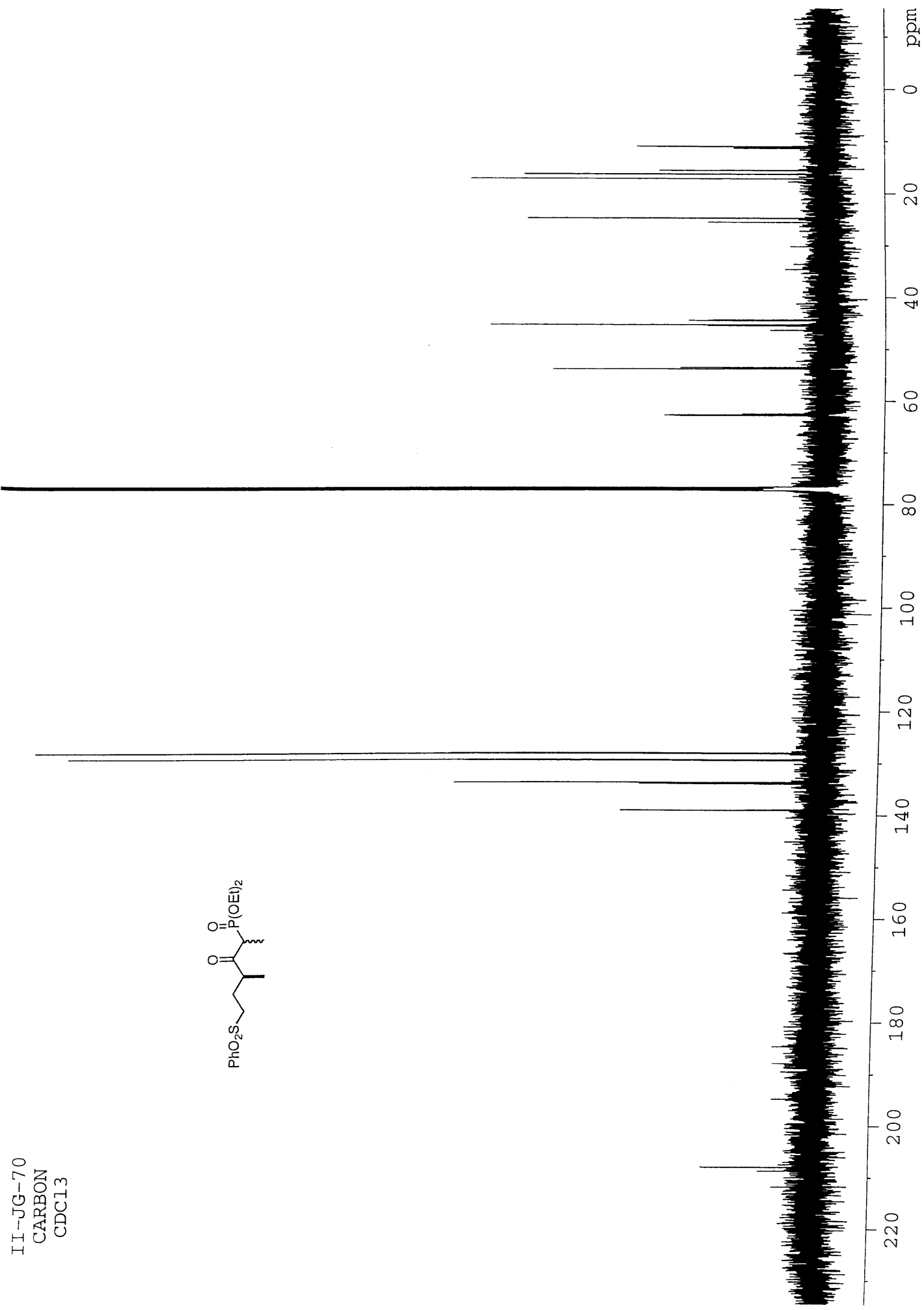
01030406: Scan 132 (24.15 min) - Back  
Base: 629.00 Int: 868125 Sample: VG 70-SE Positive Ion FAB

Sample: JG107  
Instrument Resolution: 7000  
Theoretical mass: (M+Na) 629.15936  
Measured Mass: (M+Na) 629.15857  
Error: 1.26 ppm



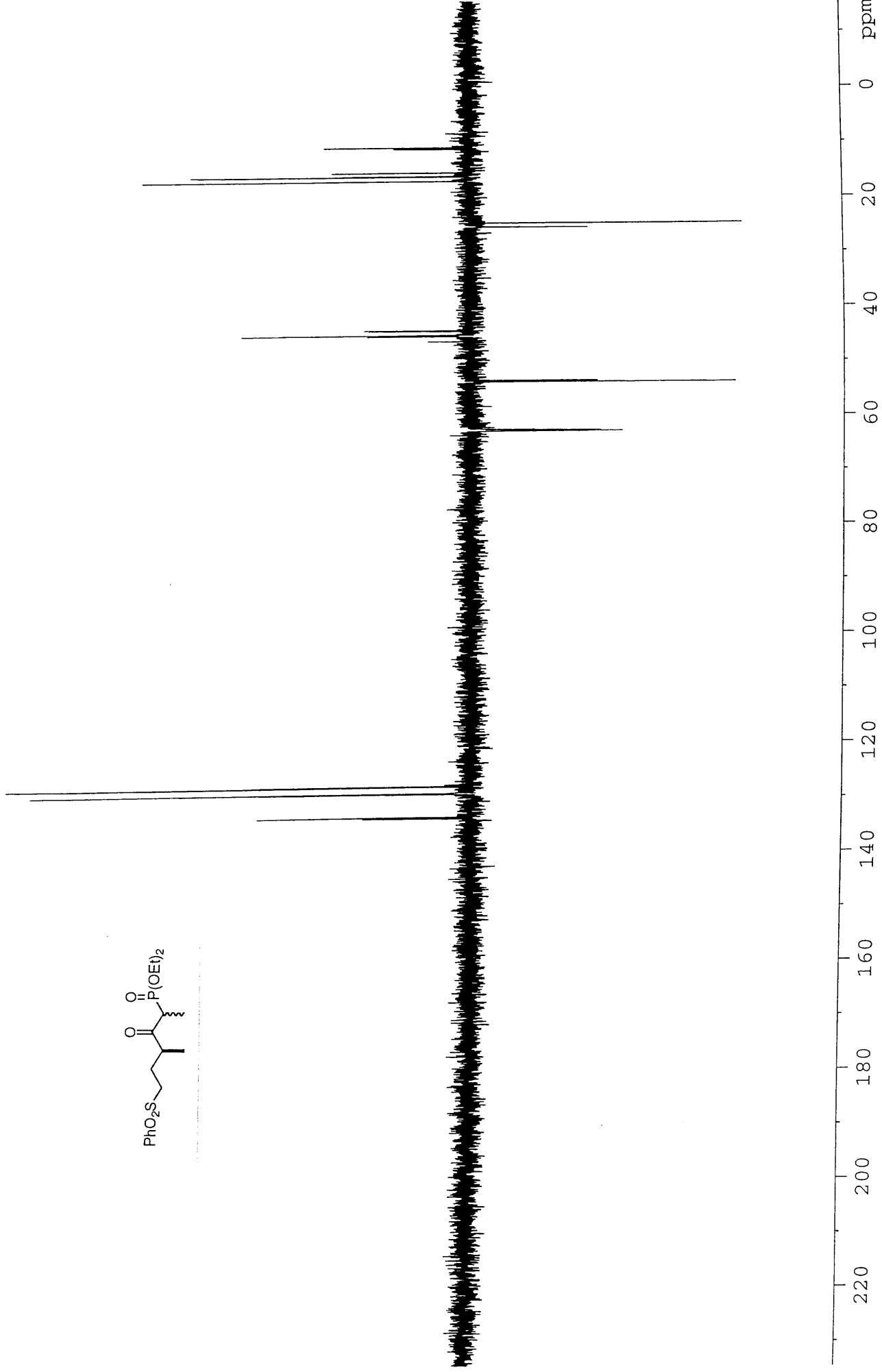
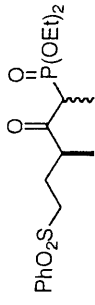
II-JG-70  
PROTON  
CDCl3



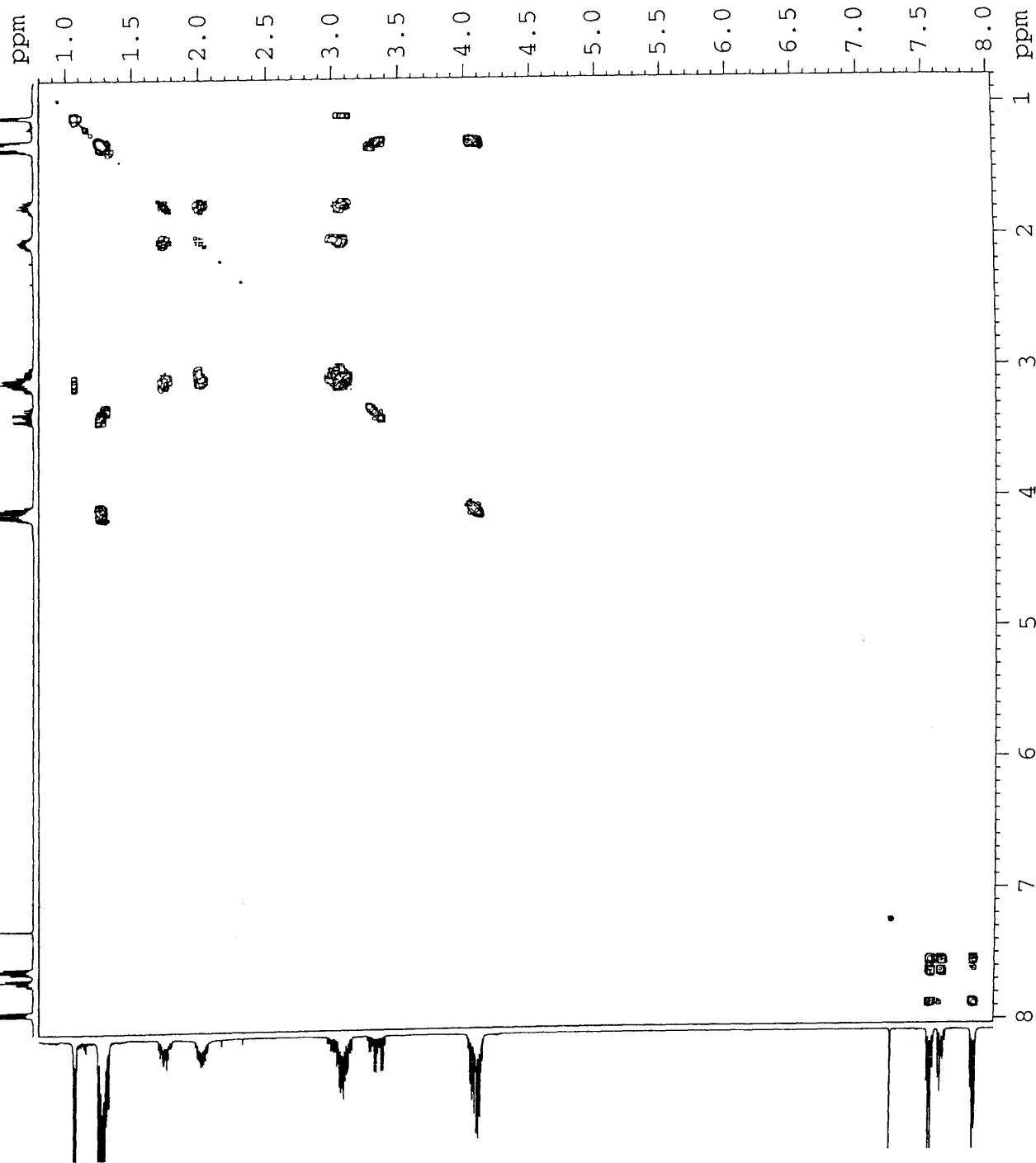
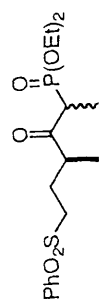


II-JG-70  
CARBON  
CDCl<sub>3</sub>

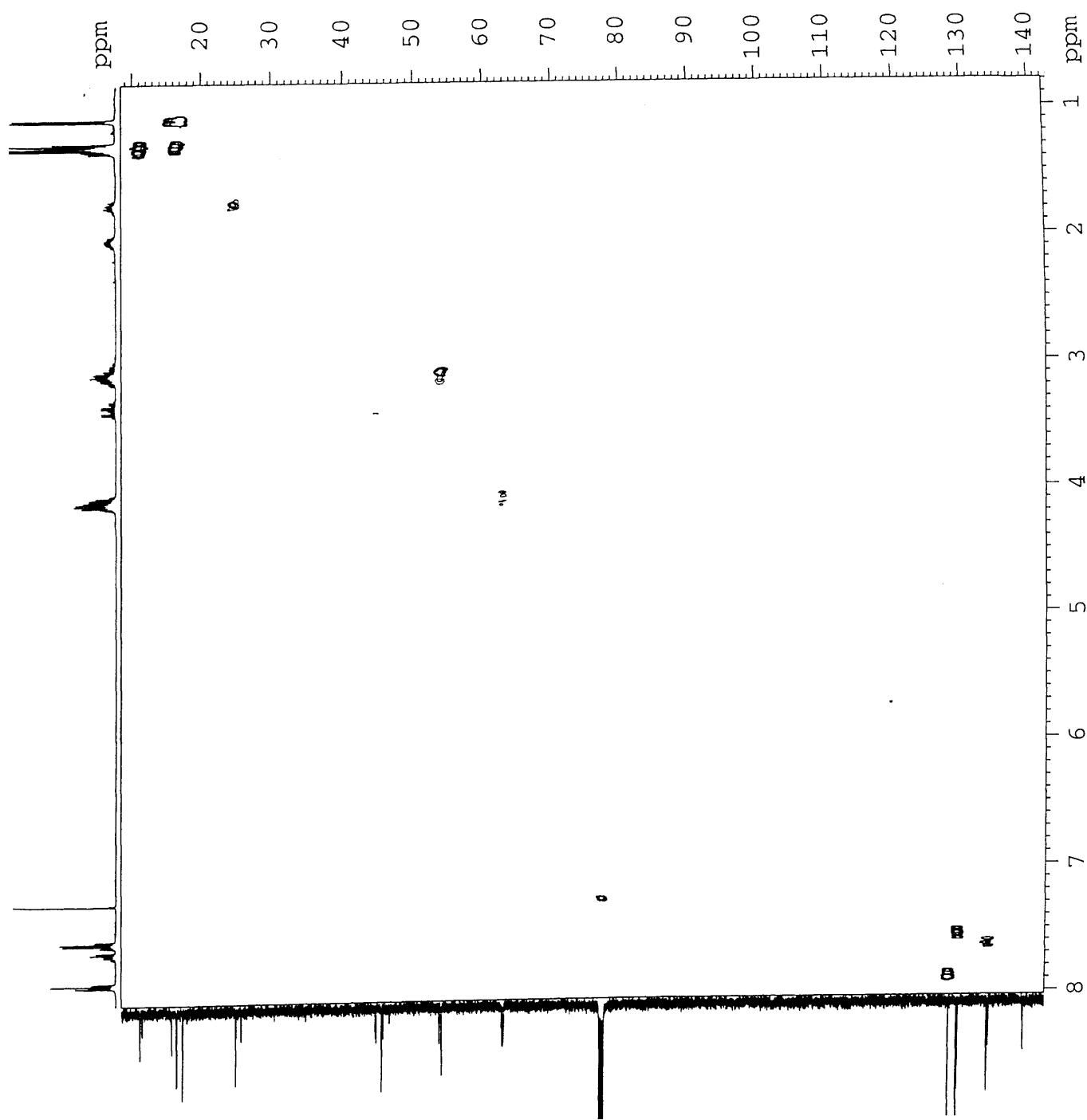
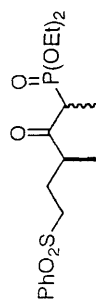
II-JG-70  
DEPT  
CDCl<sub>3</sub>

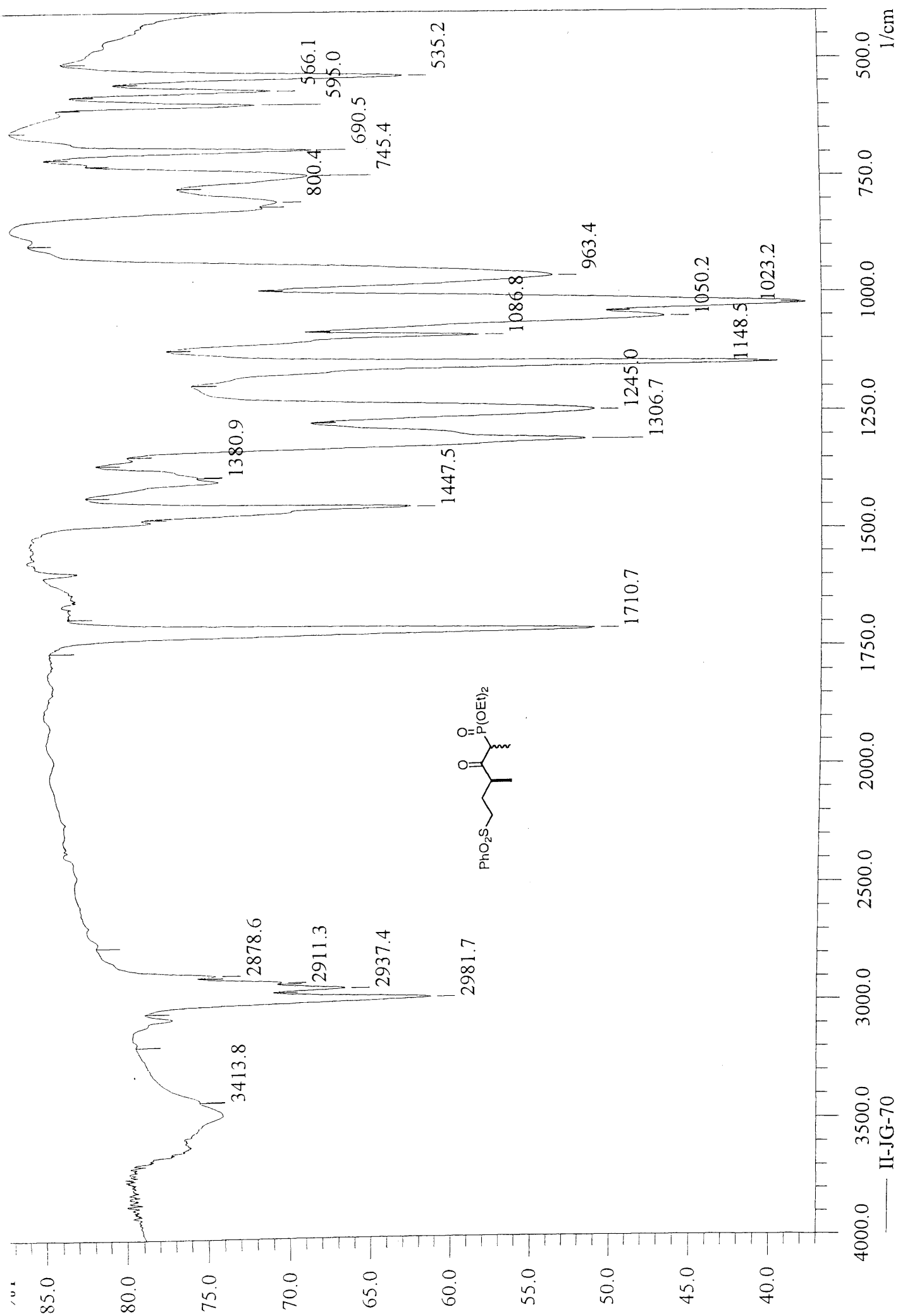


II-JG-70  
COSY  
CDCl3

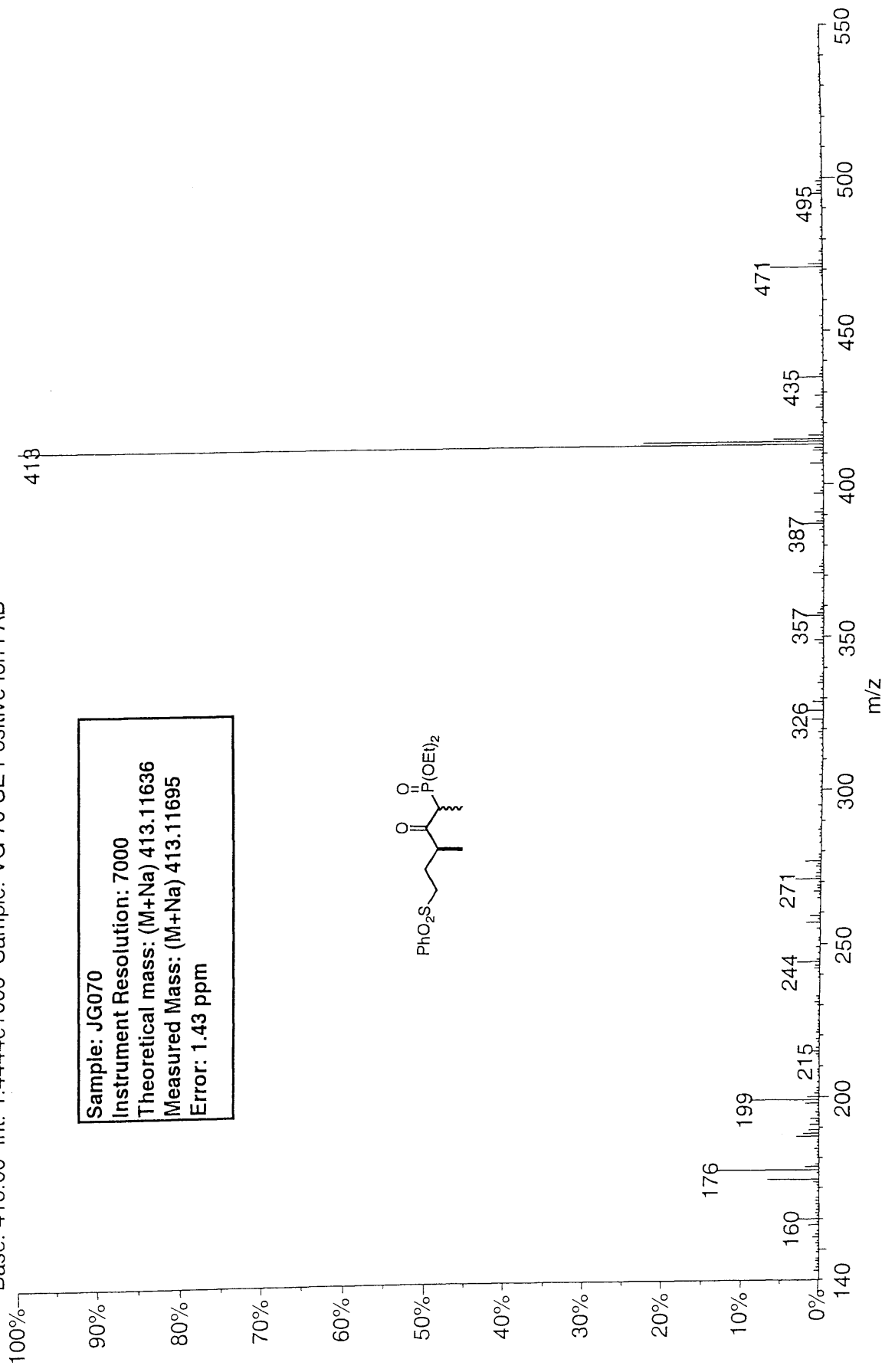


II-JG-70  
HMQC  
CDC13

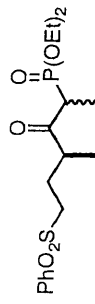




01300306: Scan Avg 311-312 (56.97 - 57.15 min) - Back  
Base: 413.00 Int: 1.4444e+006 Sample: VG 70-SE Positive Ion FAB

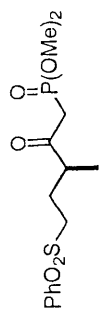


Sample: JG070  
Instrument Resolution: 7000  
Theoretical mass: (M+Na) 413.11636  
Measured Mass: (M+Na) 413.11695  
Error: 1.43 ppm

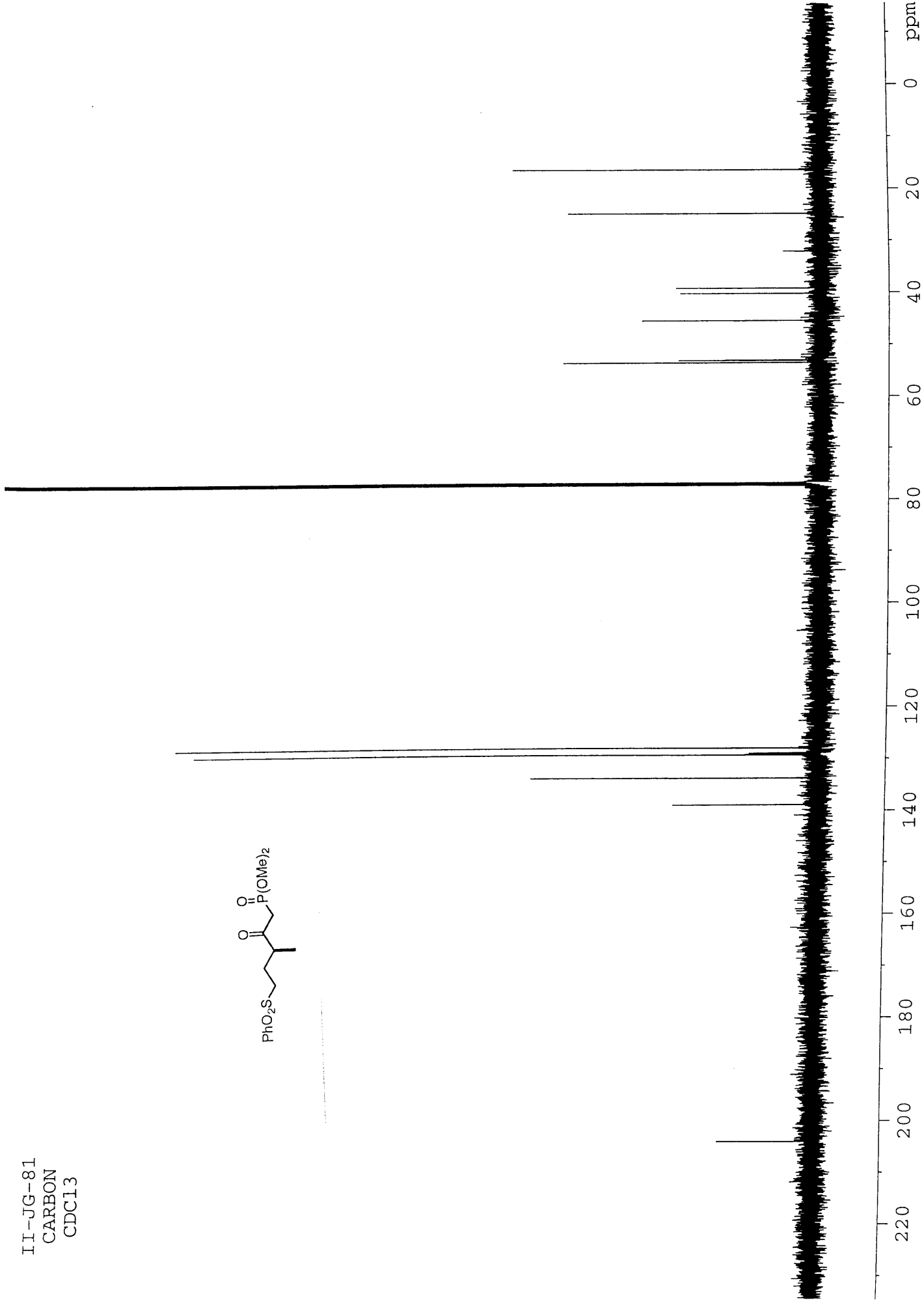
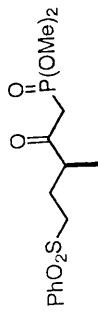


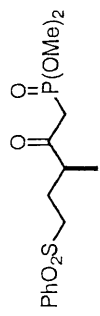


II-JG-81  
PROTON  
CDCl<sub>3</sub>

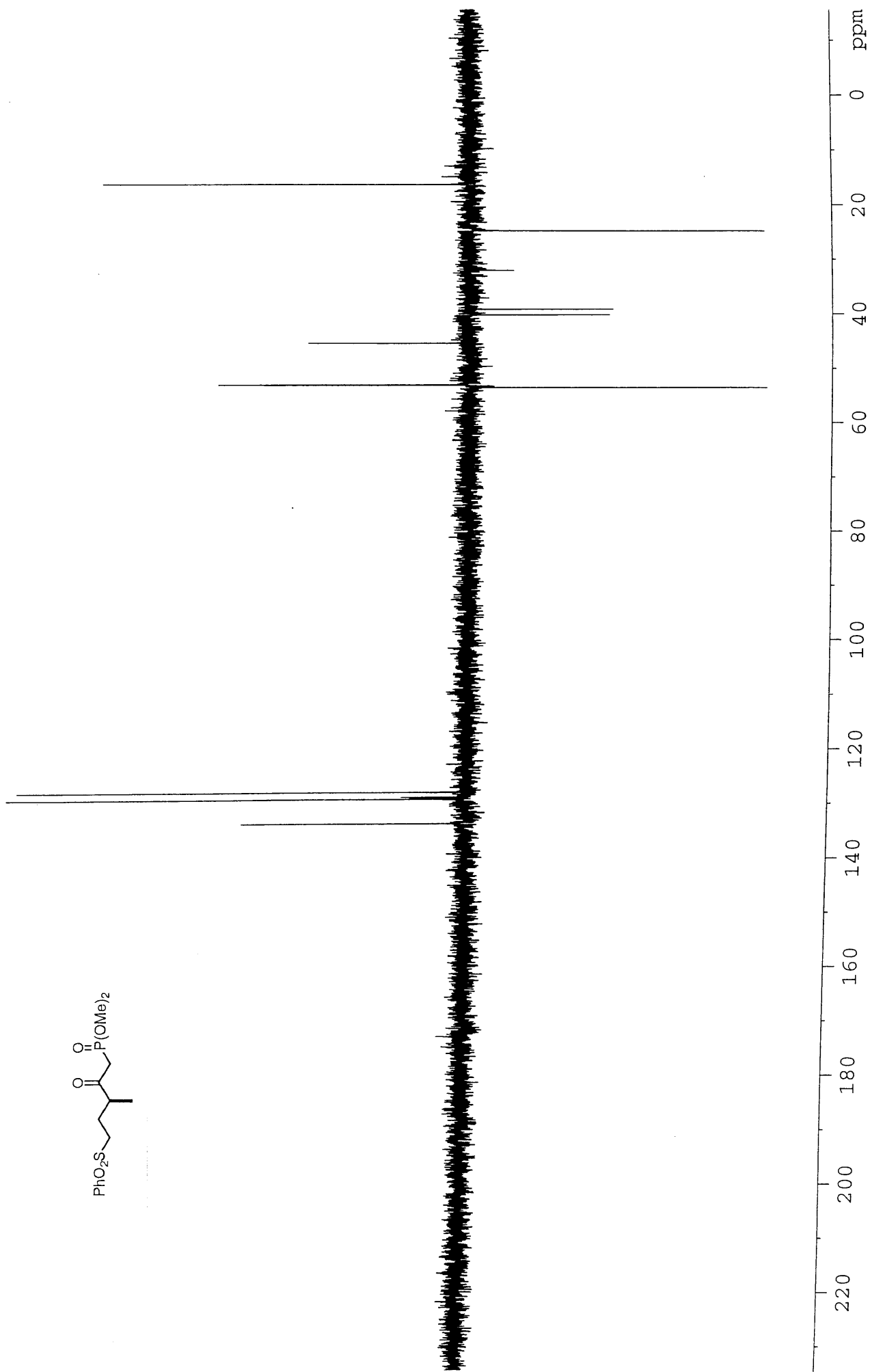


II-JG-81  
CARBON  
CDC13

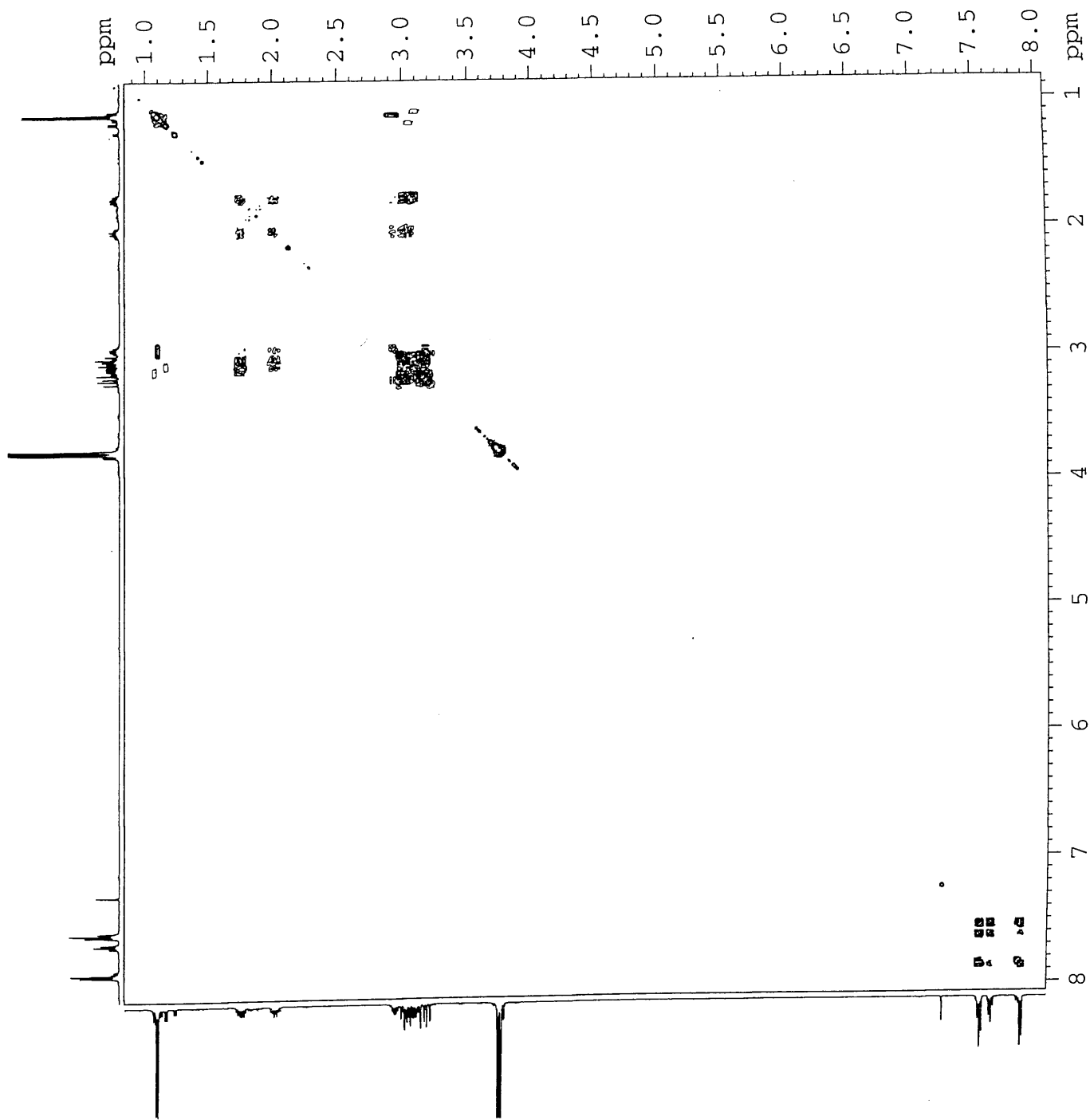
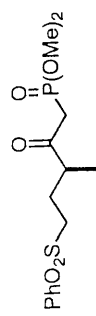




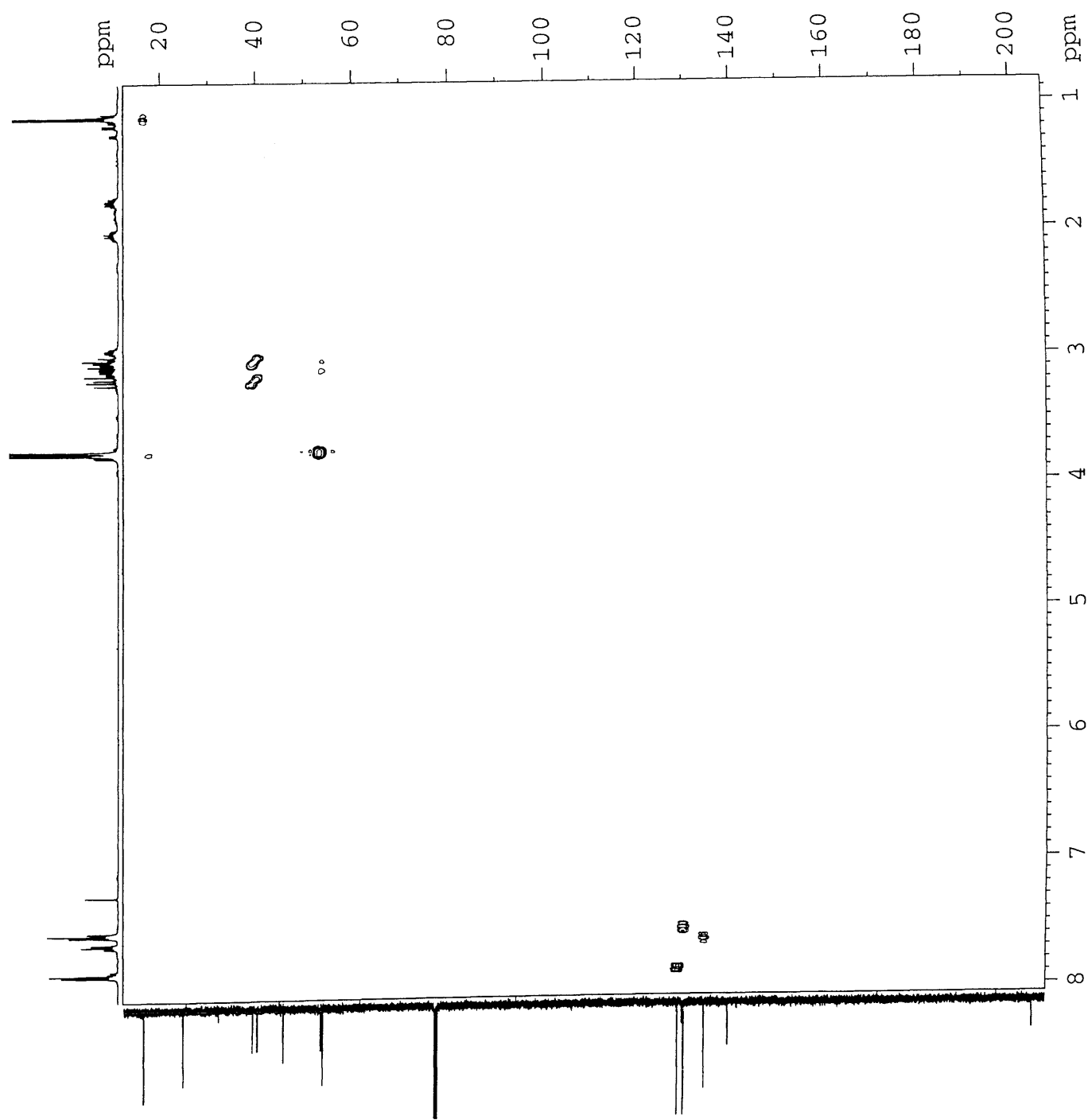
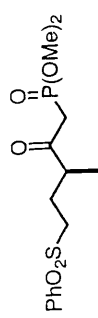
II-JG-81  
DEPT  
CDC13

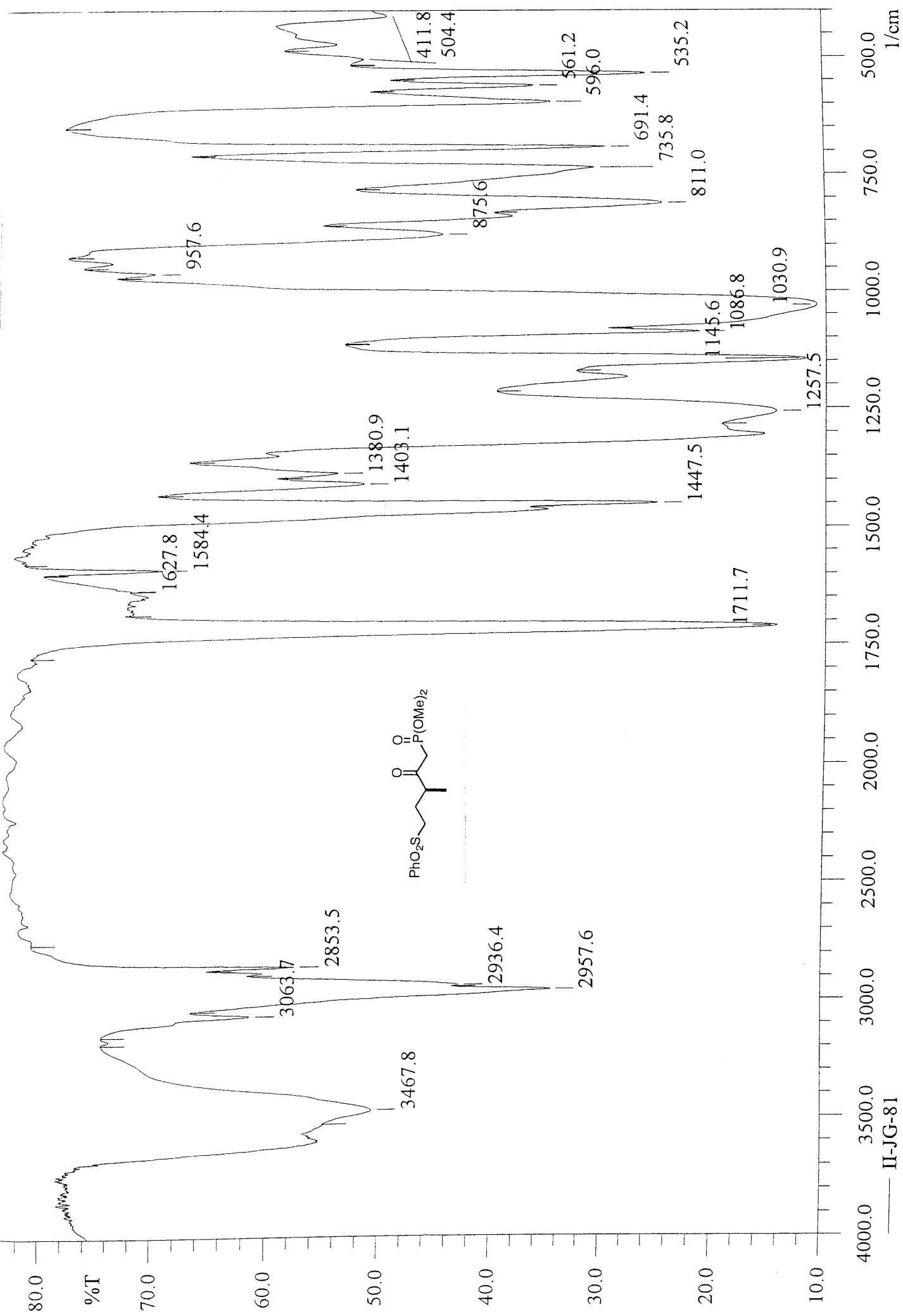


II-JG-81  
COSY  
CDC13



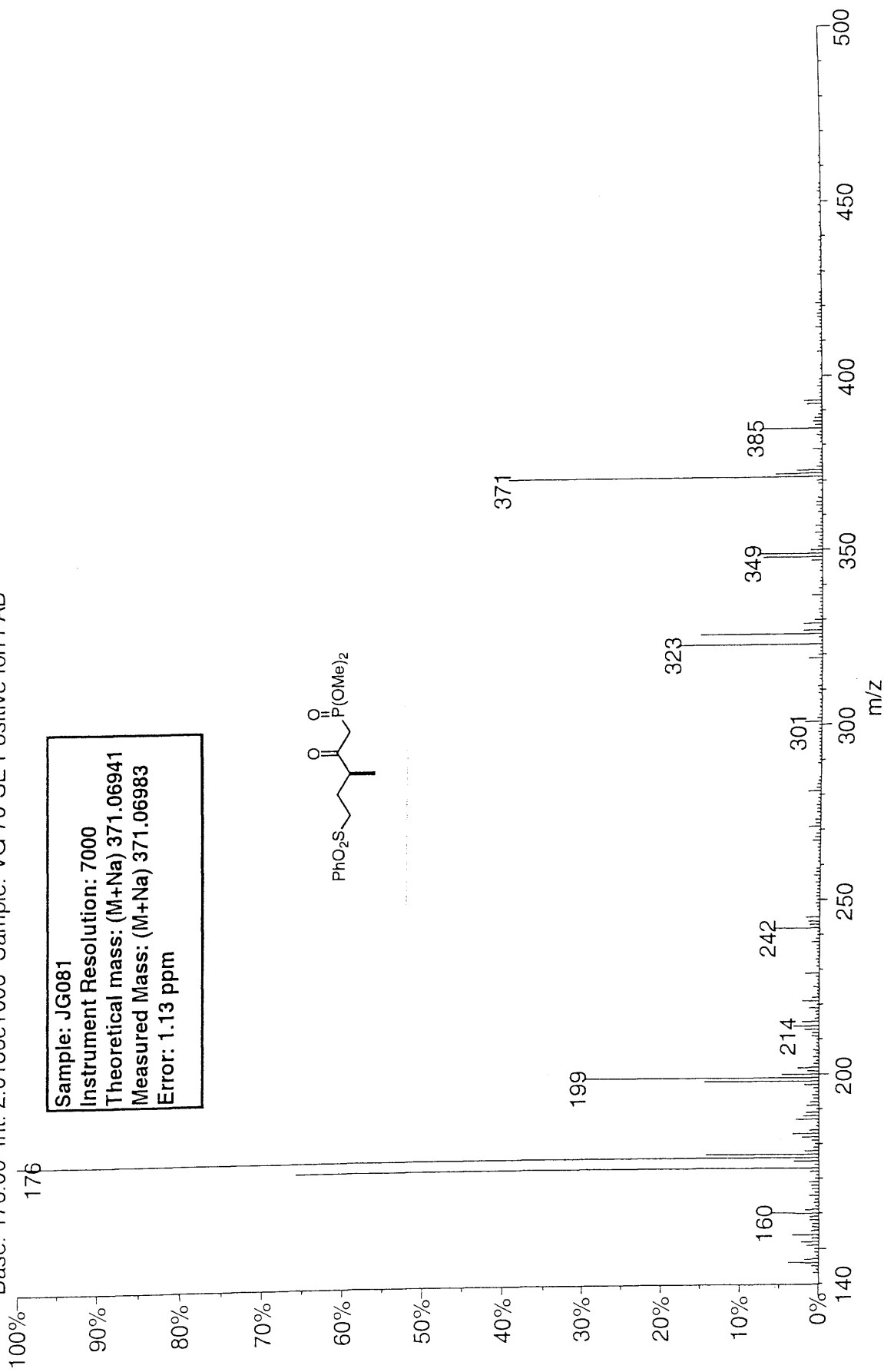
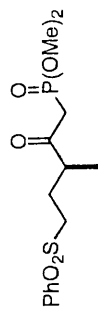
II-JG-81  
HMQC  
CDCl<sub>3</sub>





01300306: Scan 328 (60.08 min) - Back  
Base: 176.00 Int: 2.0186e+006 Sample: VG 70-SE Positive Ion FAB

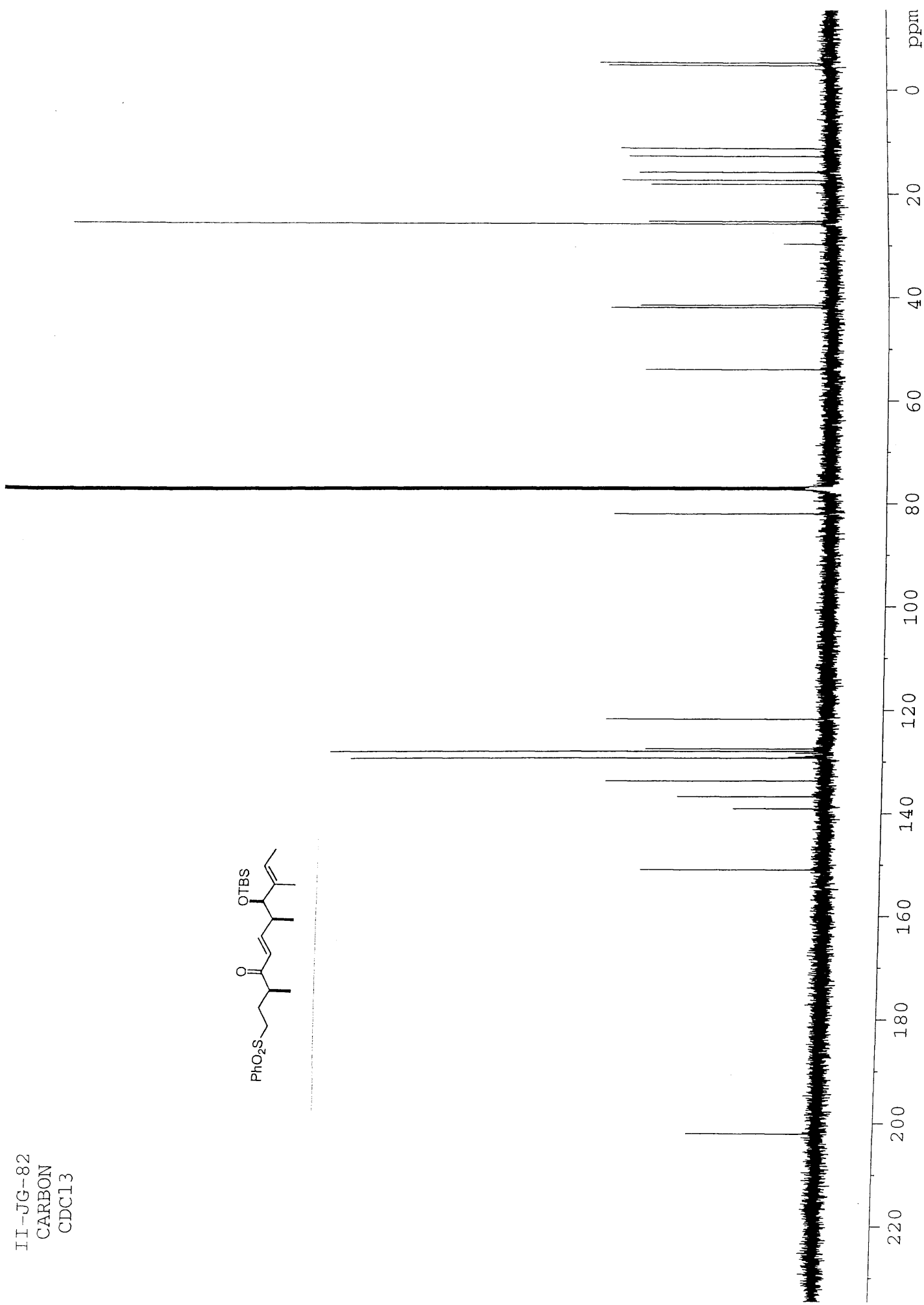
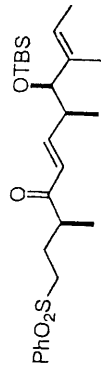
Sample: JG081  
Instrument Resolution: 7000  
Theoretical mass: (M+Na) 371.06941  
Measured Mass: (M+Na) 371.06983  
Error: 1.13 ppm



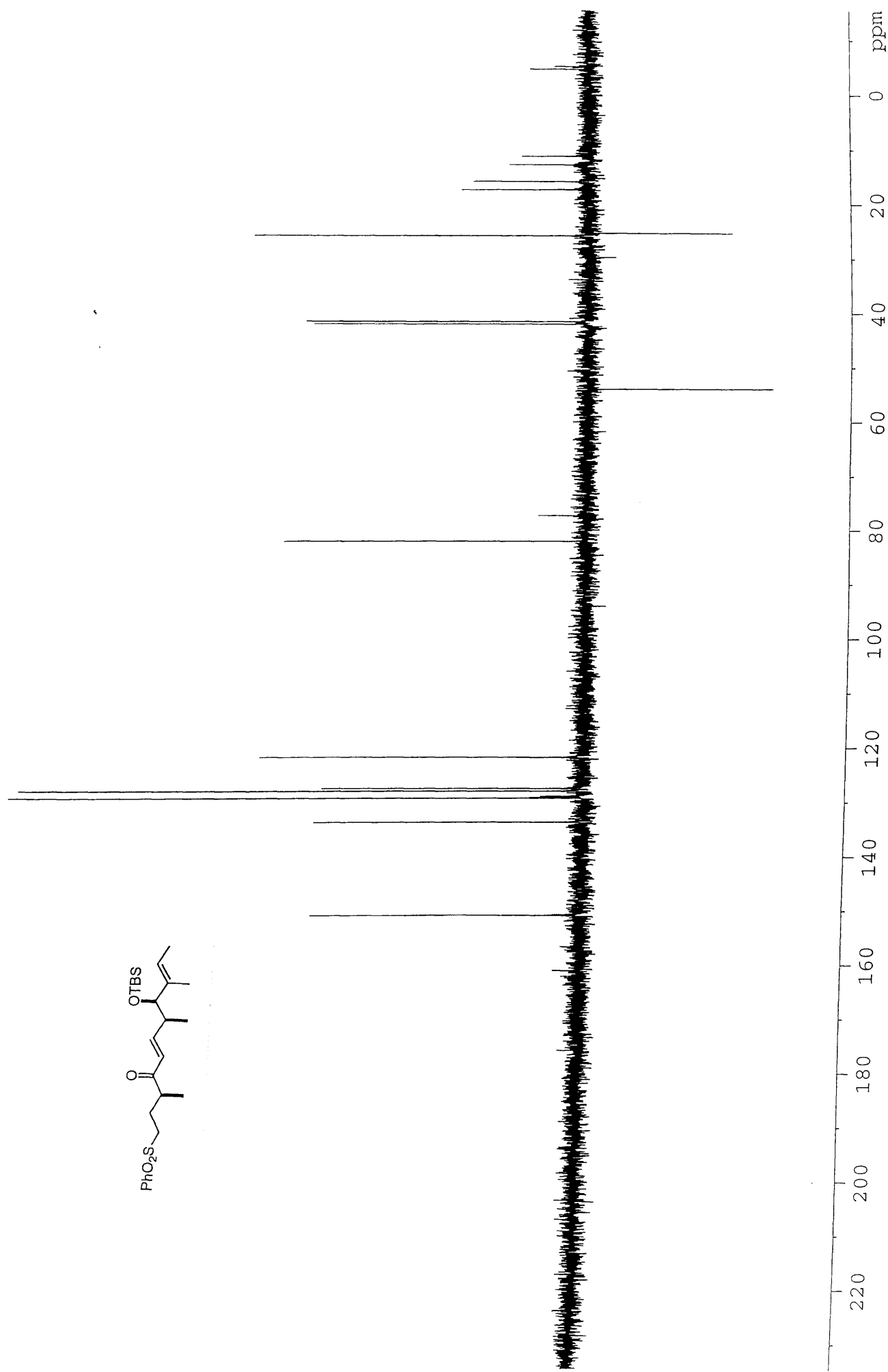
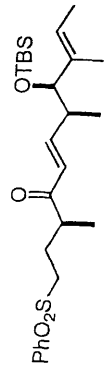




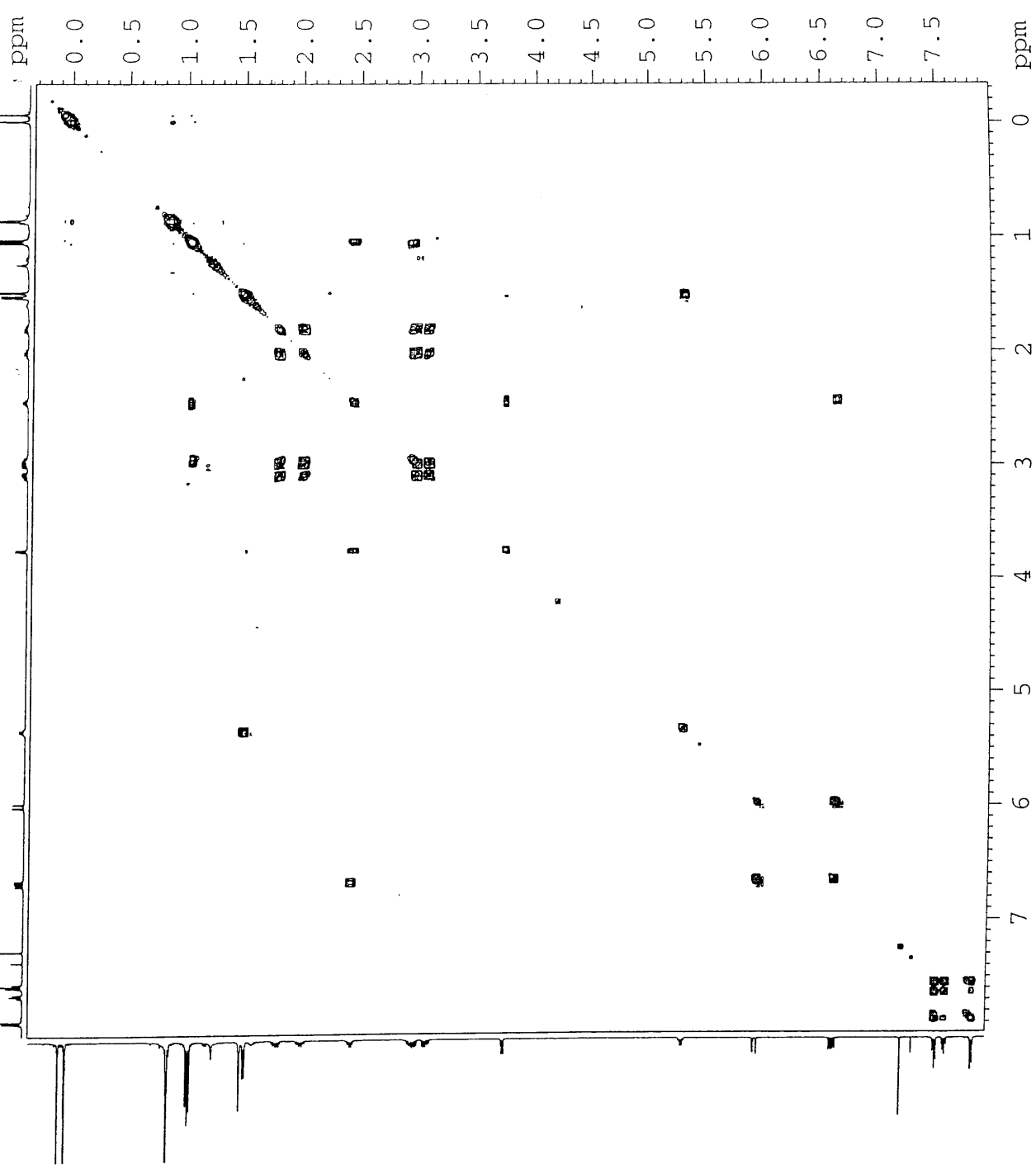
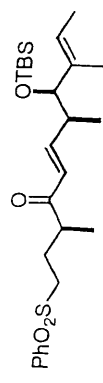
II-JG-82  
CARBON  
CDCl<sub>3</sub>



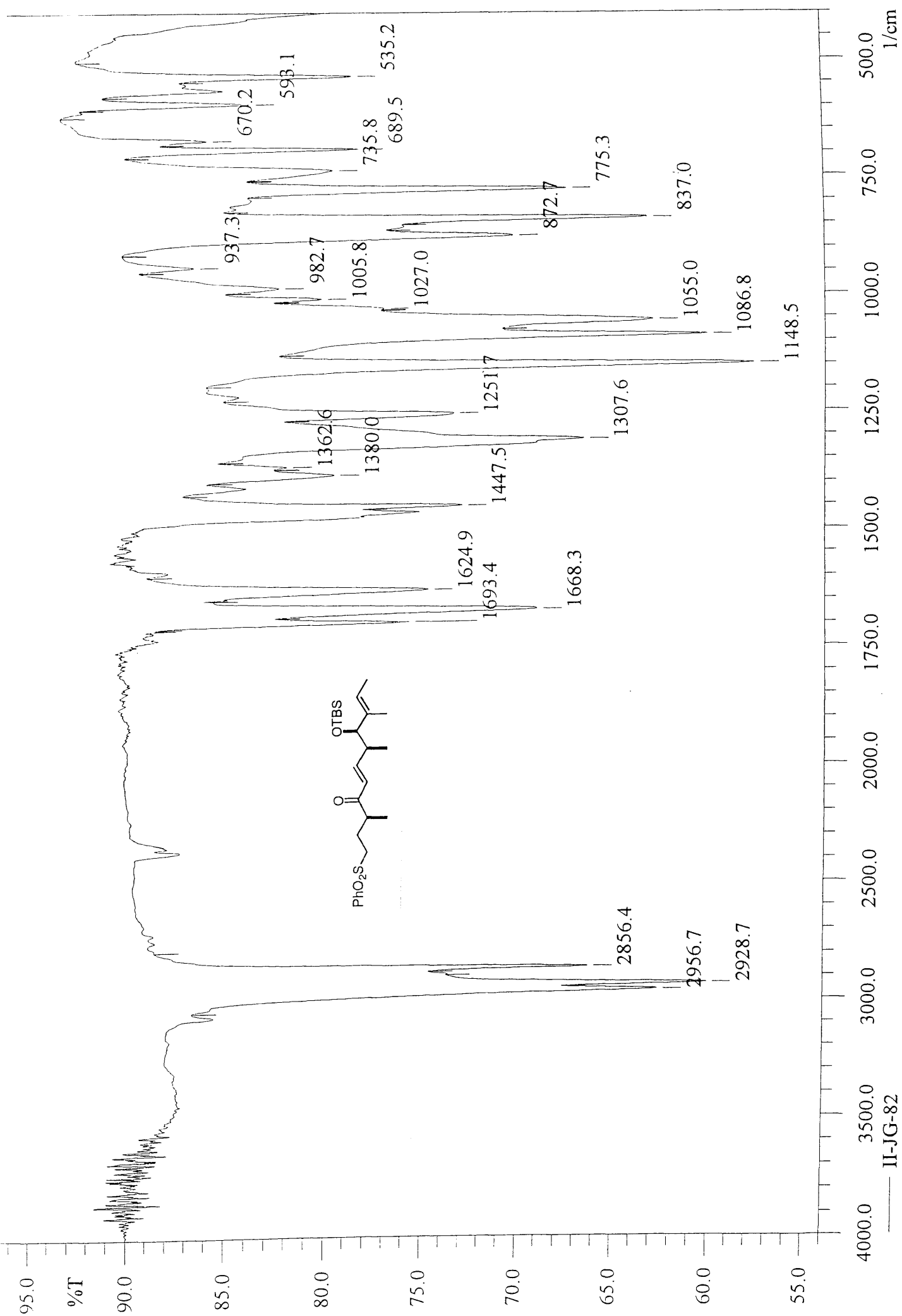
II-JG-82  
DEPT  
CDCl<sub>3</sub>



II-JG-82  
COSY  
CDC13

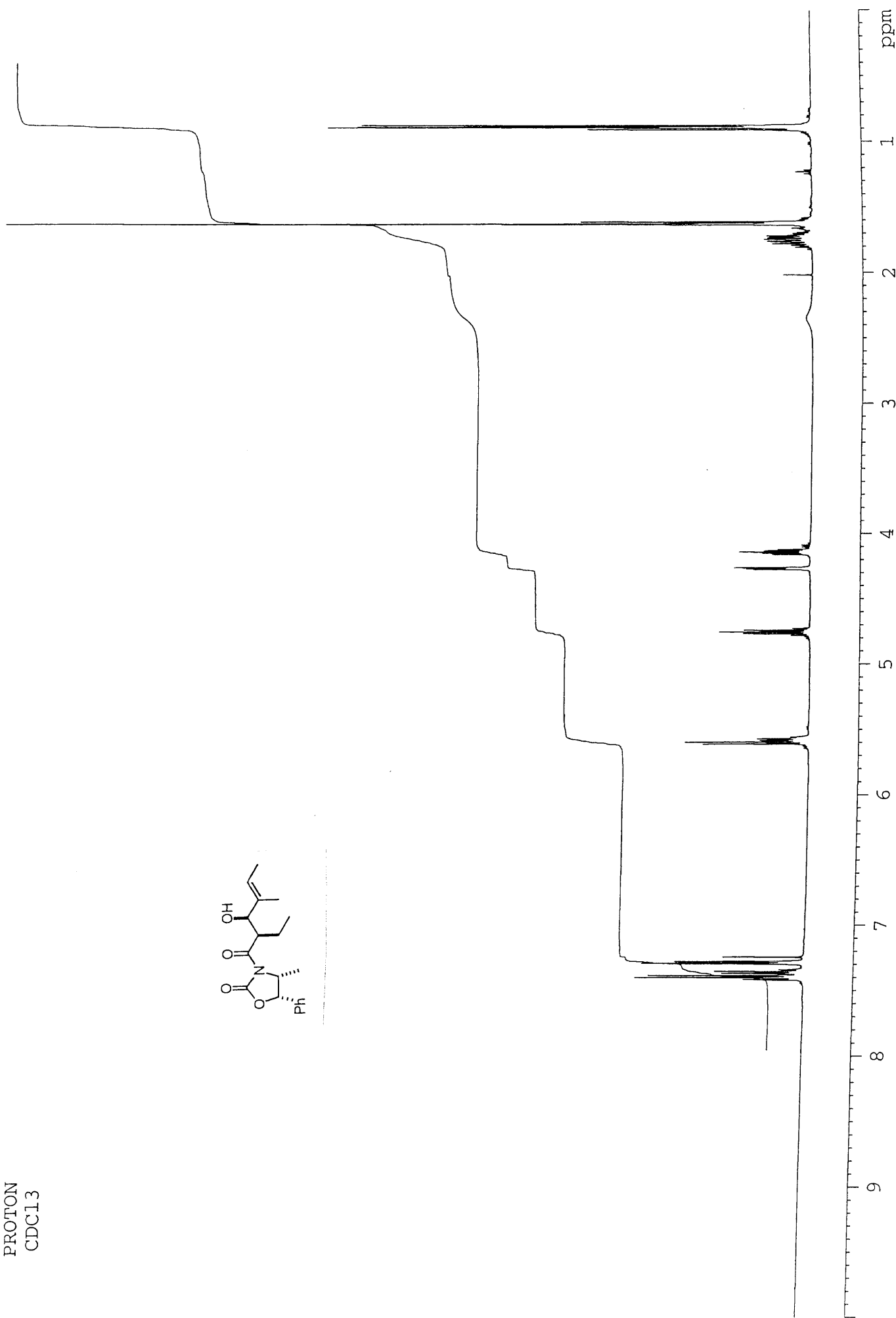
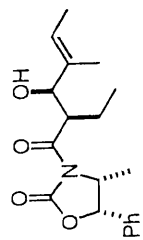




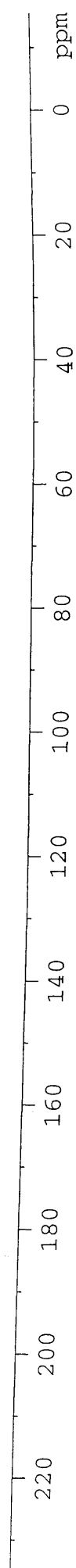
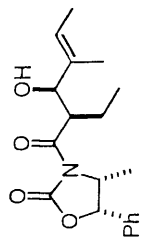




IV-JG-7  
PROTON  
CDCl3

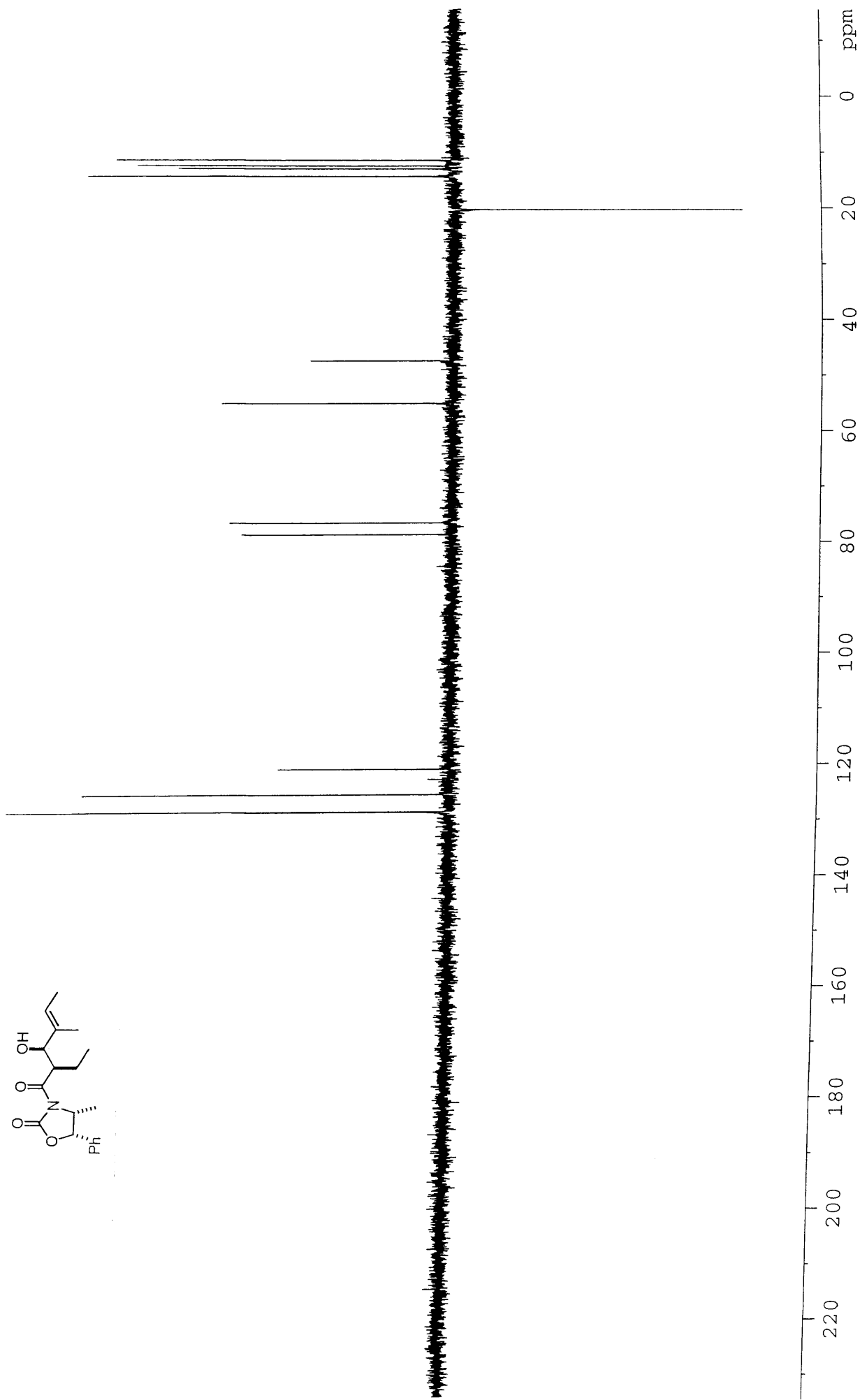
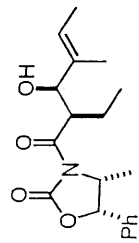


IV-JG--7  
CARBON  
CDCl<sub>3</sub>

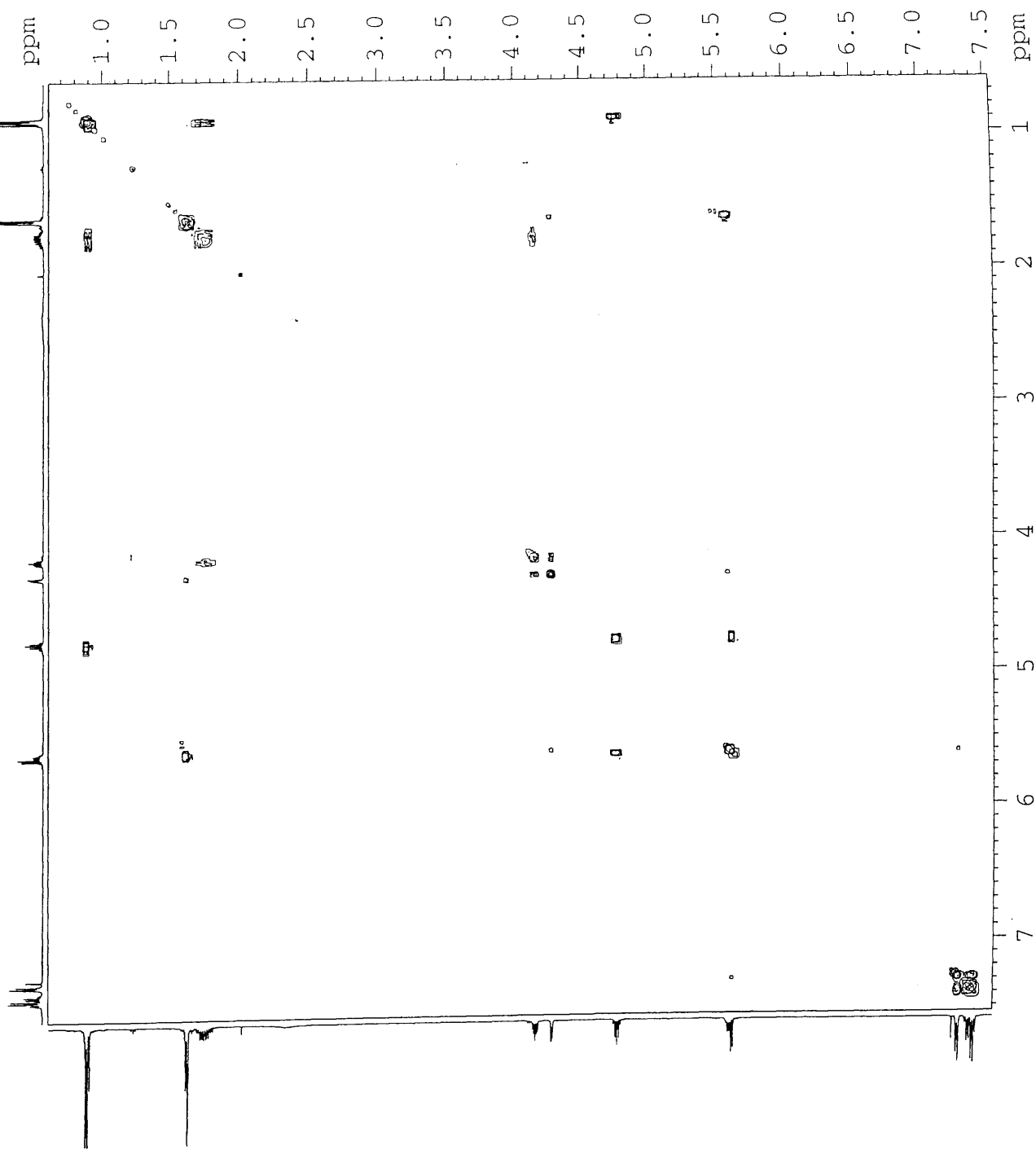
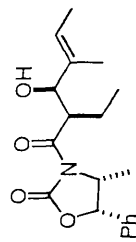


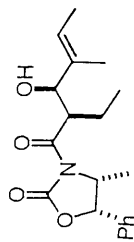


IV-JG-7  
DEPT  
CDCl<sub>3</sub>

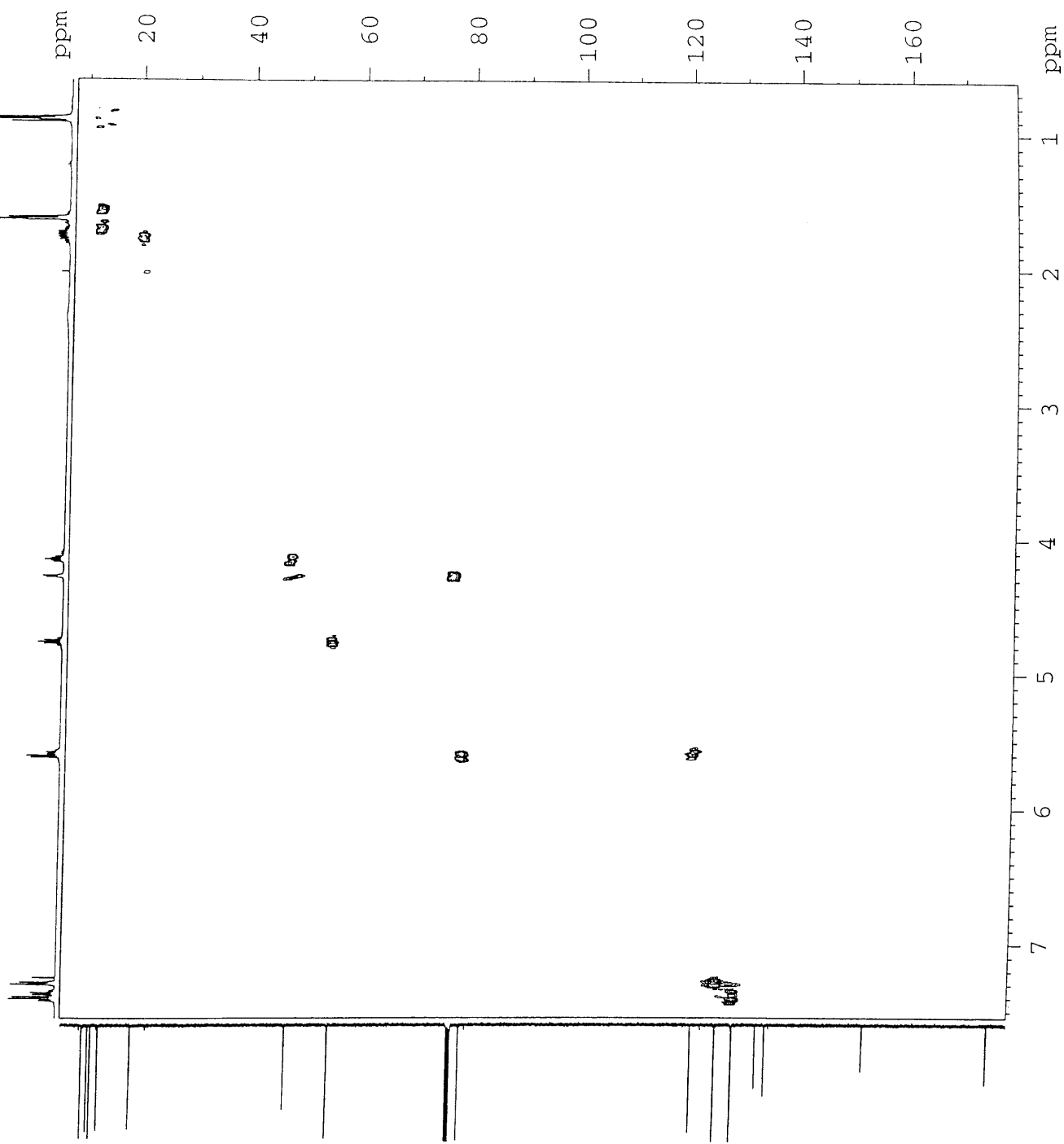


IV-JG-7  
COSY  
CDCl<sub>3</sub>

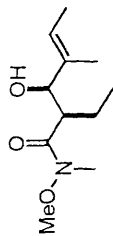




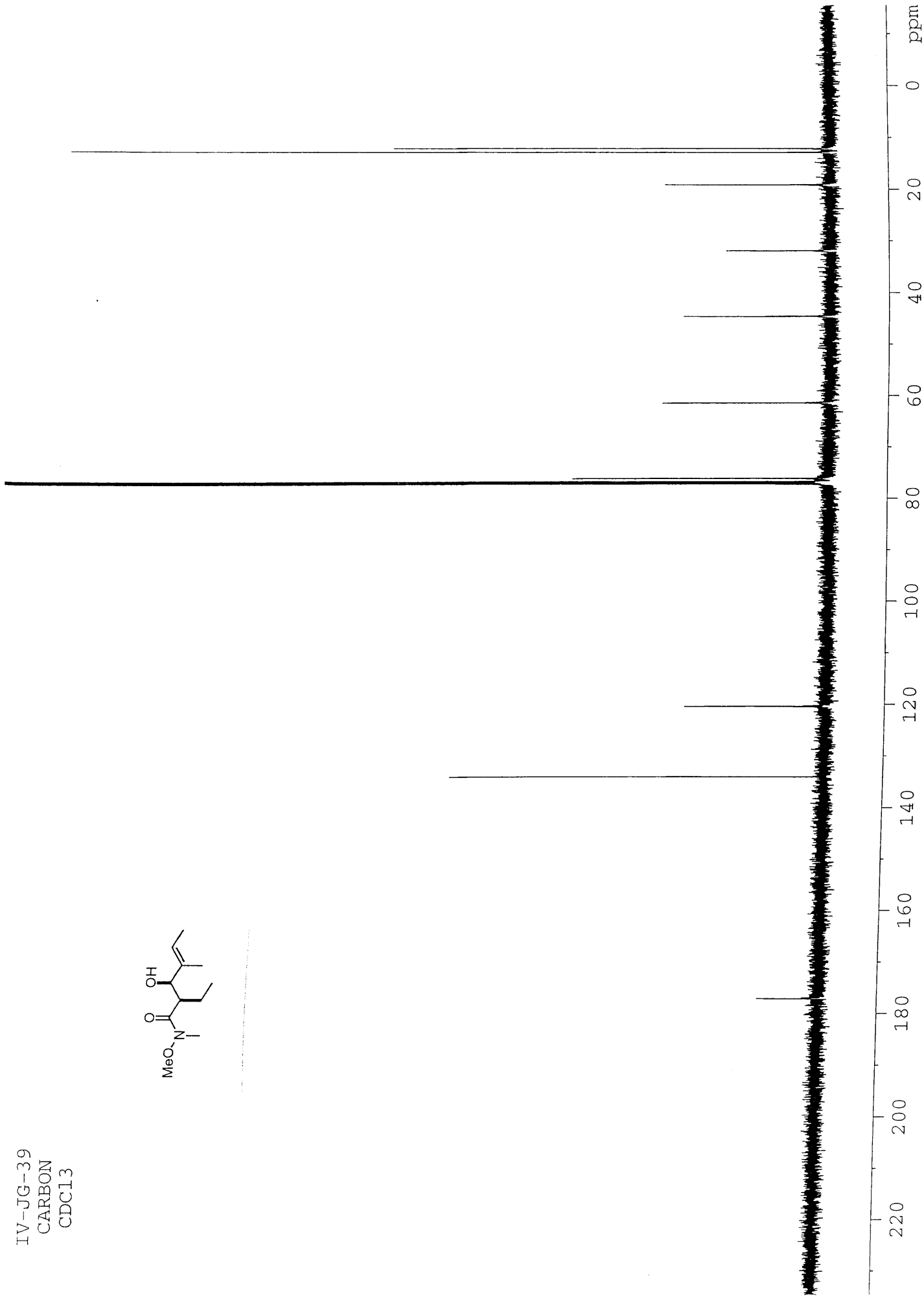
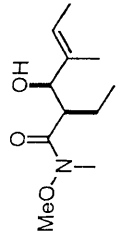
Chemical structure: 1-((S)-2-ethyl-3-hydroxy-3-methylbut-3-en-1-yl)-2-phenyl-1,3-oxazolidin-4-one



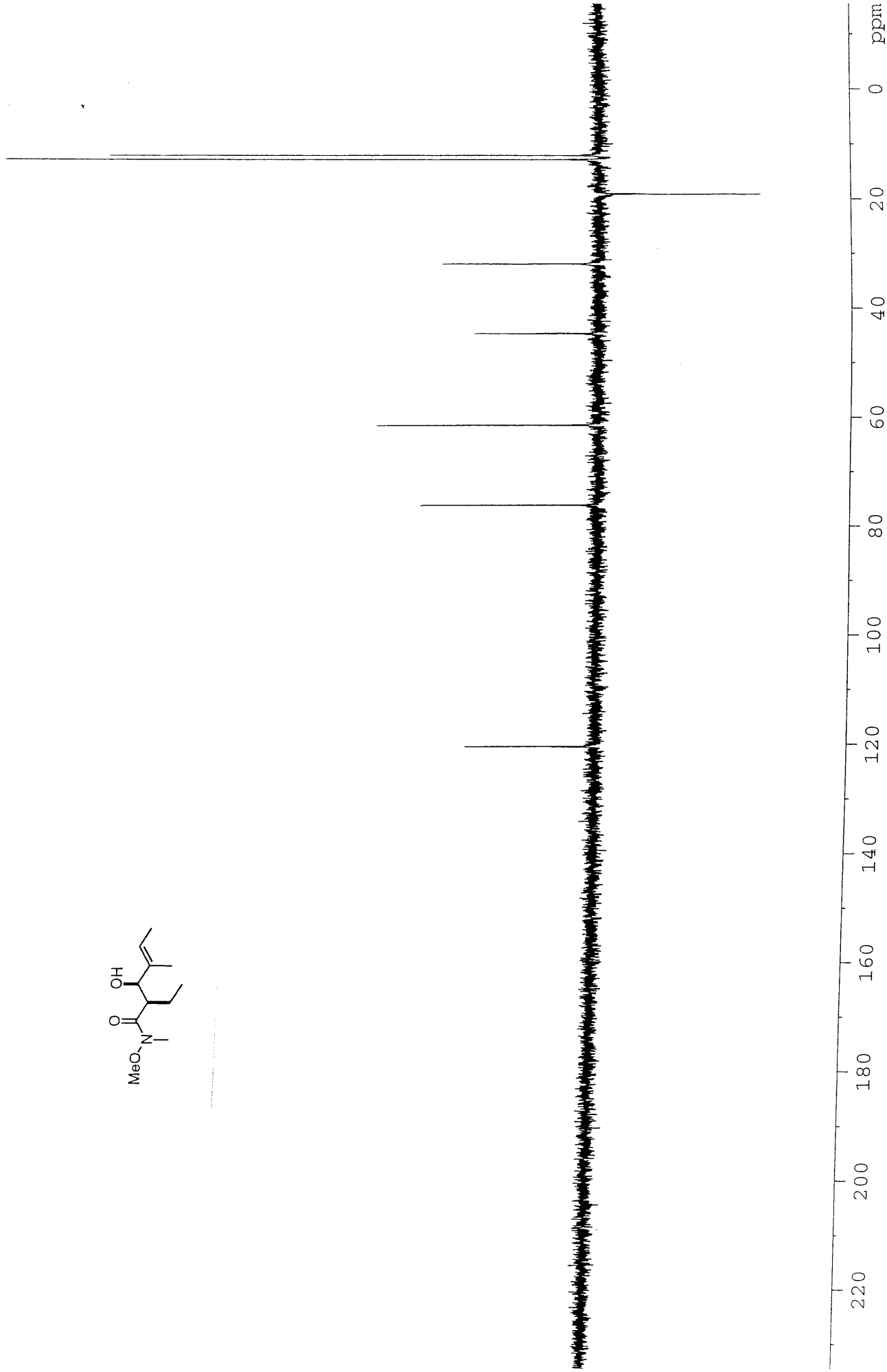
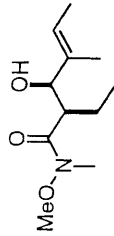
IV-JG-39  
PROTON  
CDCl<sub>3</sub>



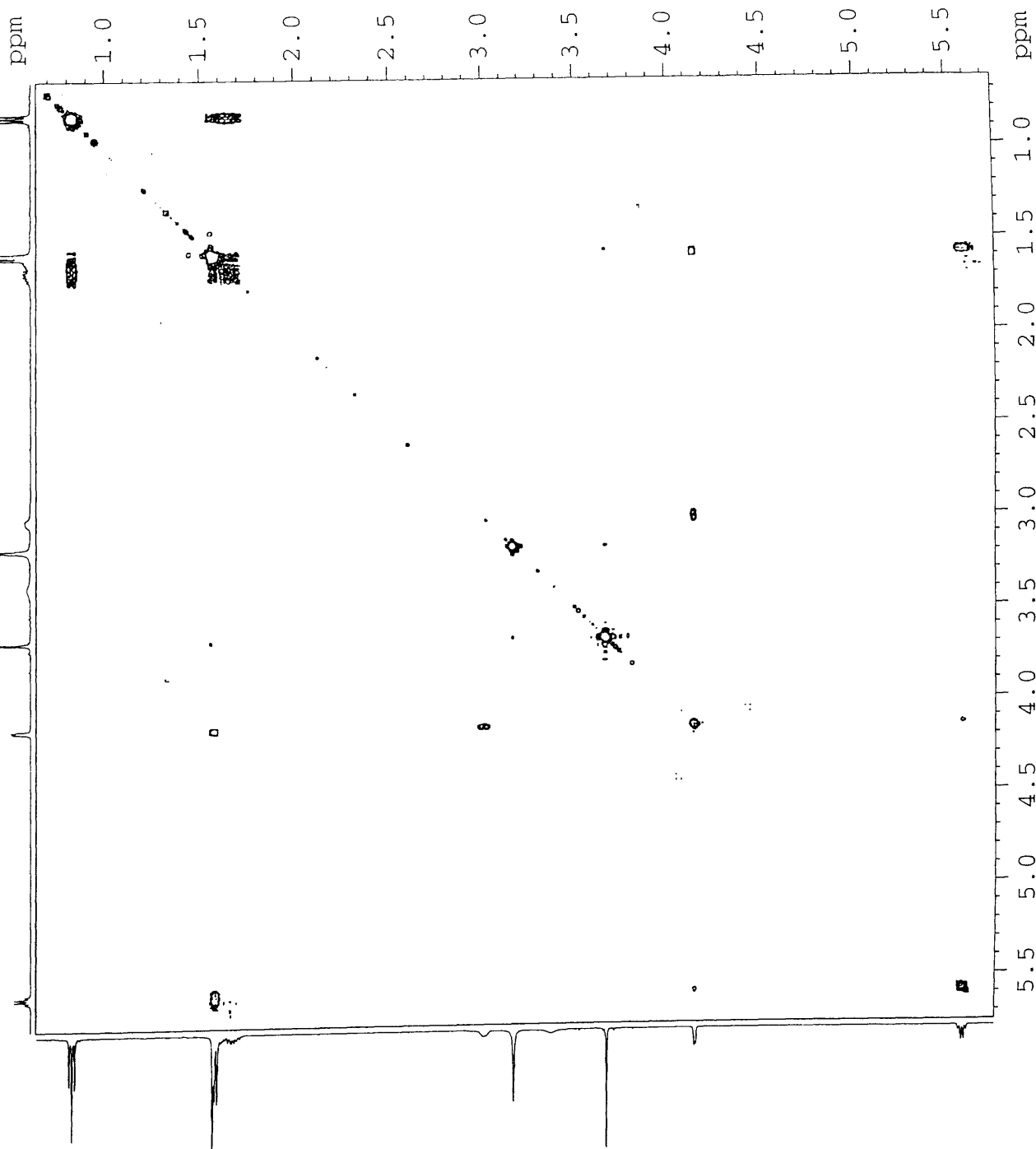
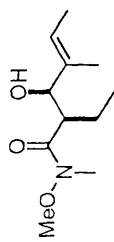
IV-JG-39  
CARBON  
CDCl<sub>3</sub>



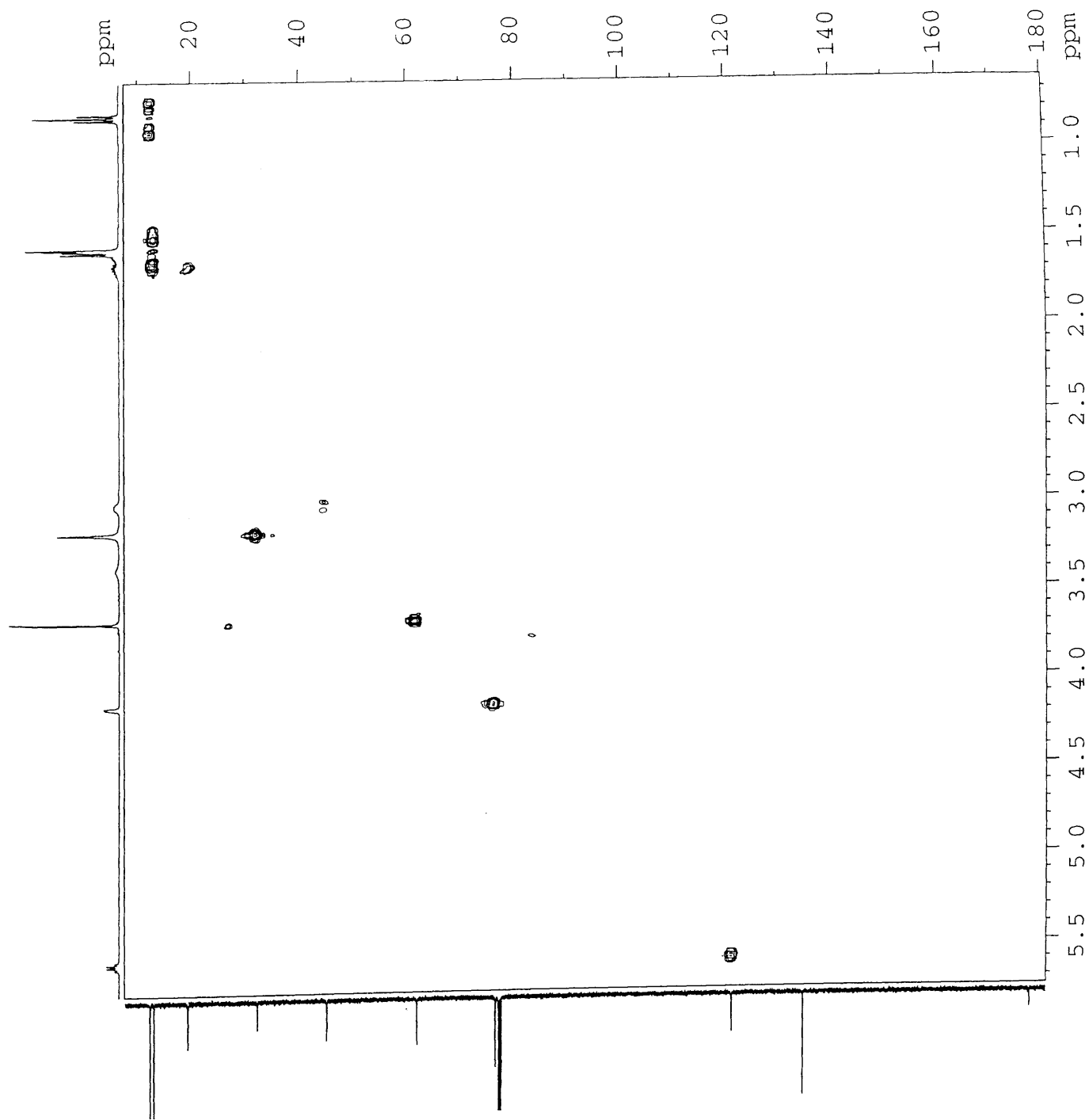
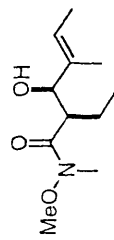
IV-JG-39  
DEPT  
CDCl<sub>3</sub>



IV-JG-39  
COSY  
CDCl3



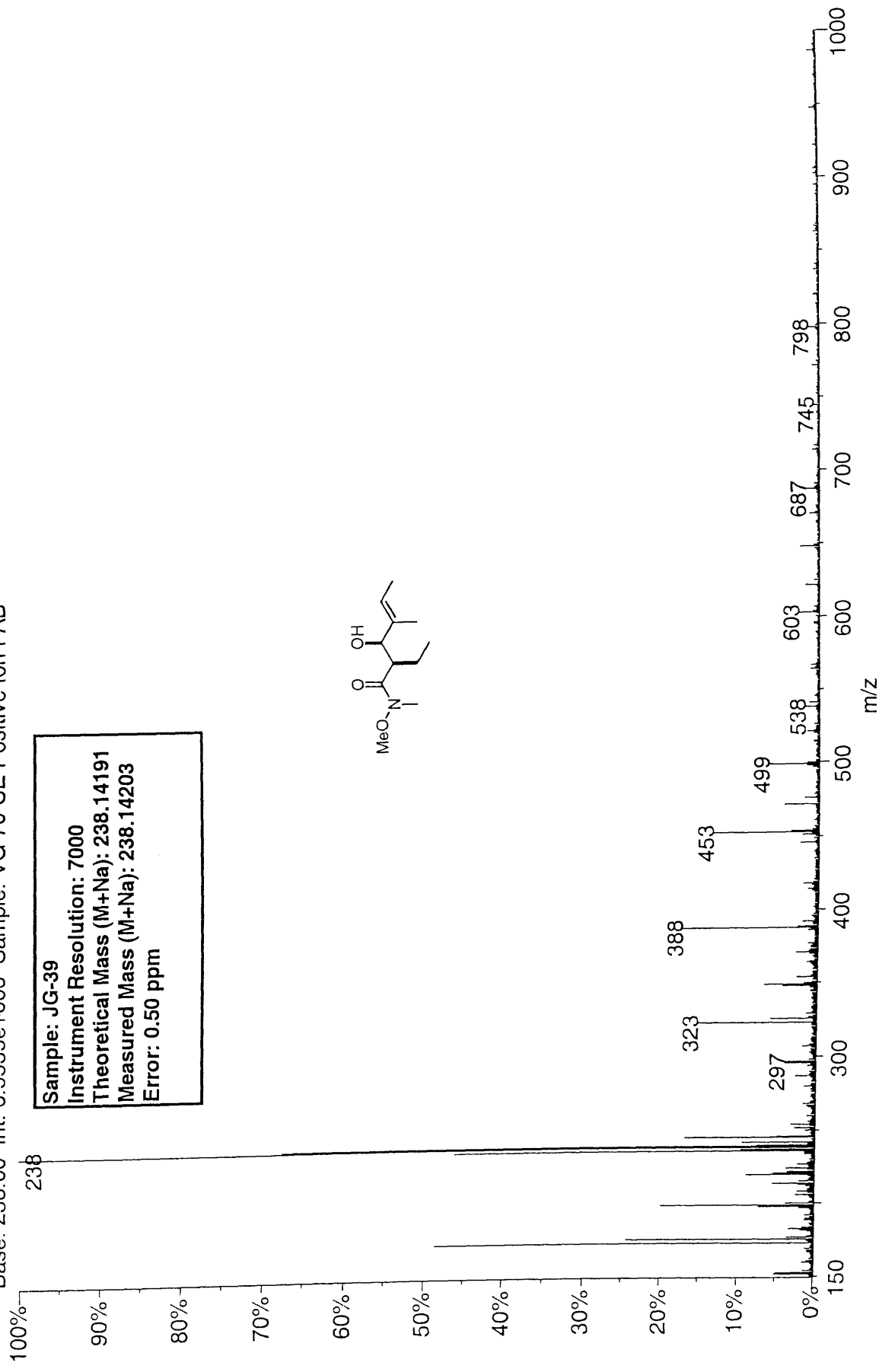
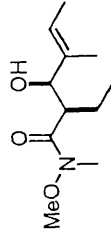
IV-JG-39  
HMQC  
CDCl<sub>3</sub>



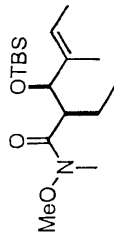


02170706: Scan Avg 321-323 (64.10 - 64.50 min)  
Base: 238.00 Int: 6.5535e+006 Sample: VG 70-SE Positive Ion FAB

Sample: JG-39  
Instrument Resolution: 7000  
Theoretical Mass (M+Na): 238.14191  
Measured Mass (M+Na): 238.14203  
Error: 0.50 ppm



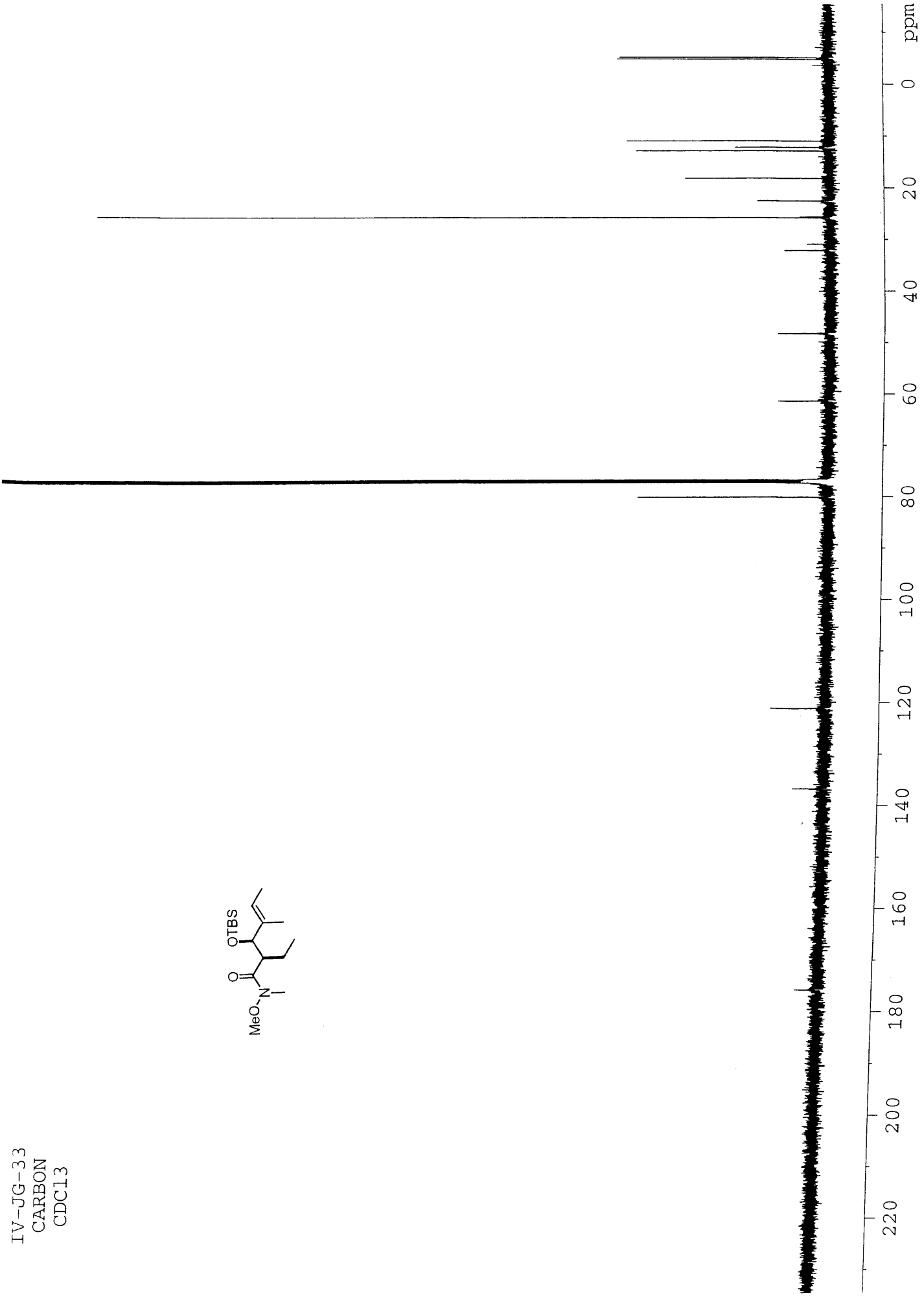
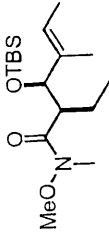
IV-JG-33  
PROTON  
CDC13



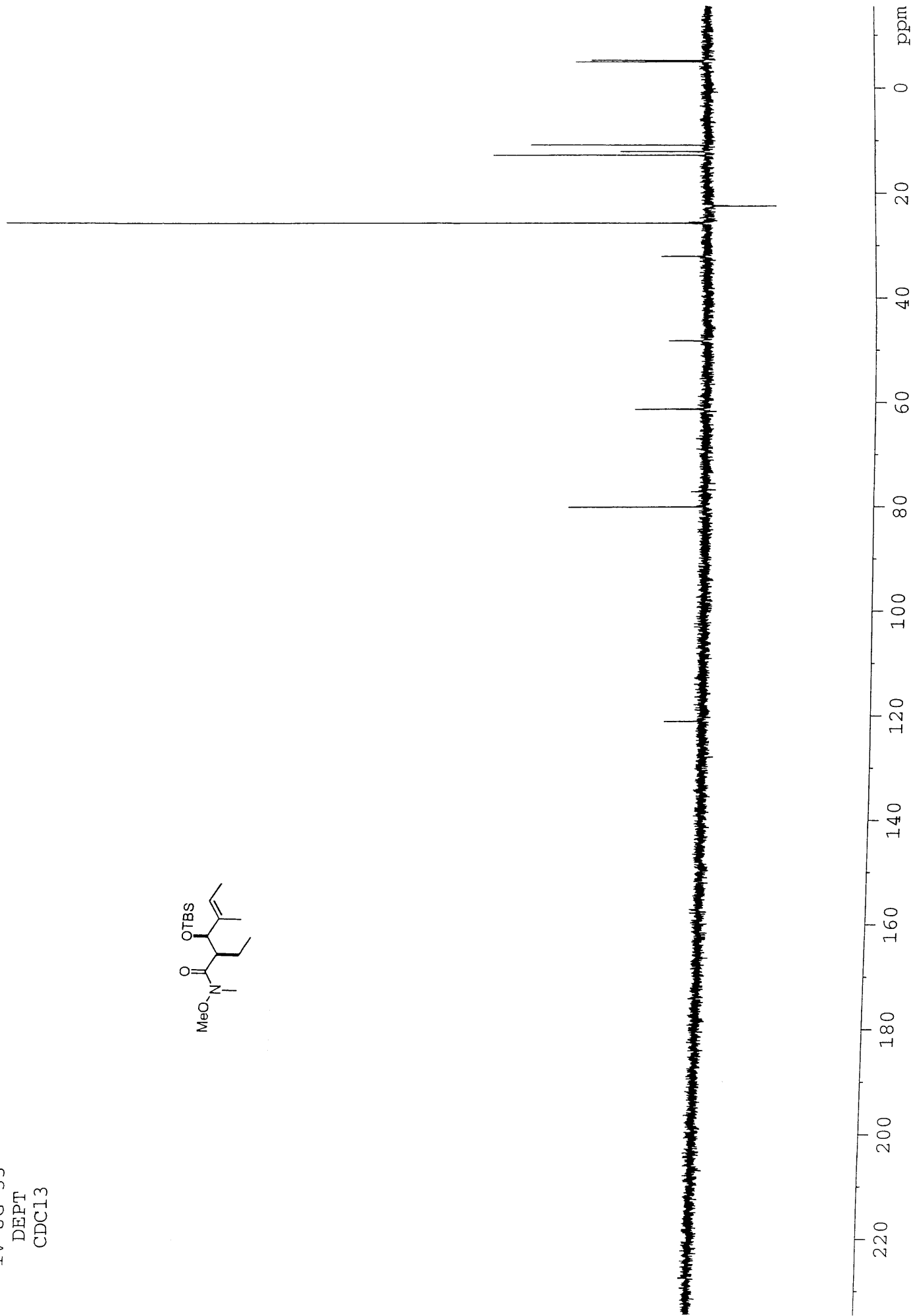
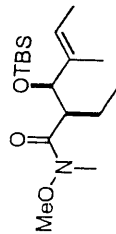
IV-JG-33

# CARBON

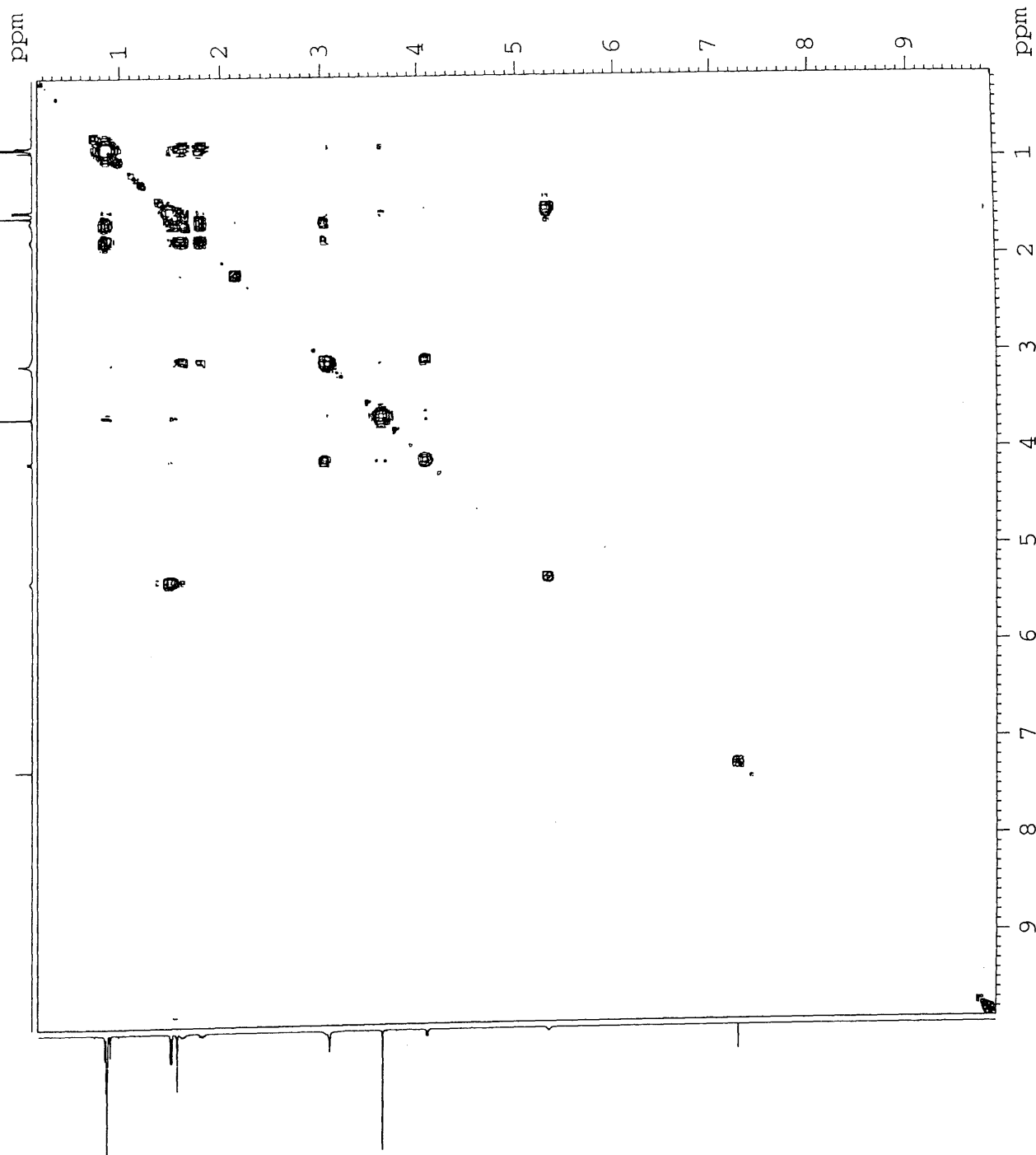
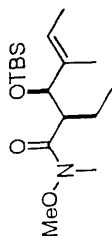
CDC13



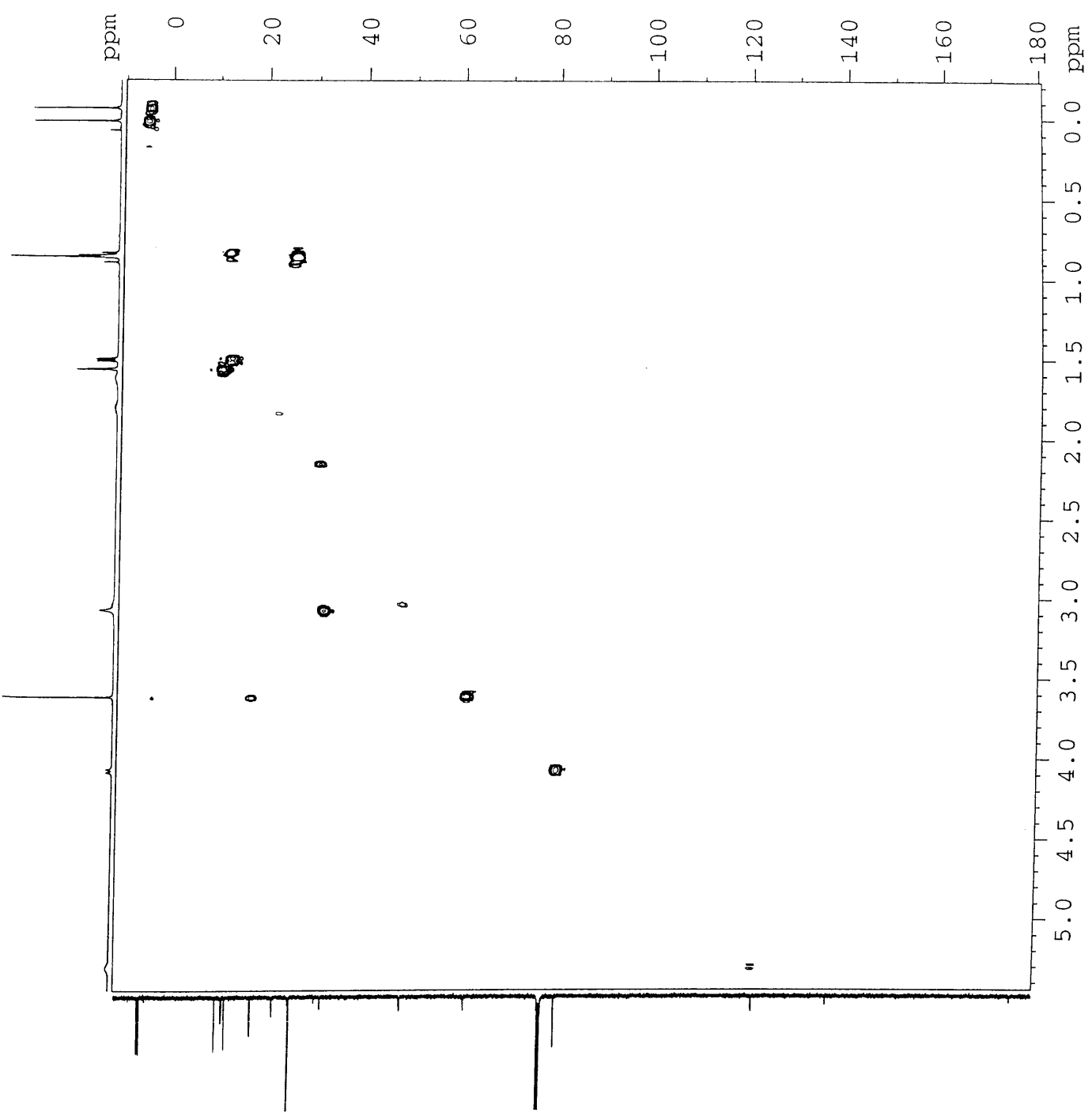
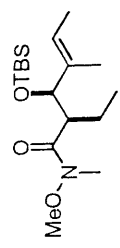
IV-JG-33  
DEPT  
CDC13

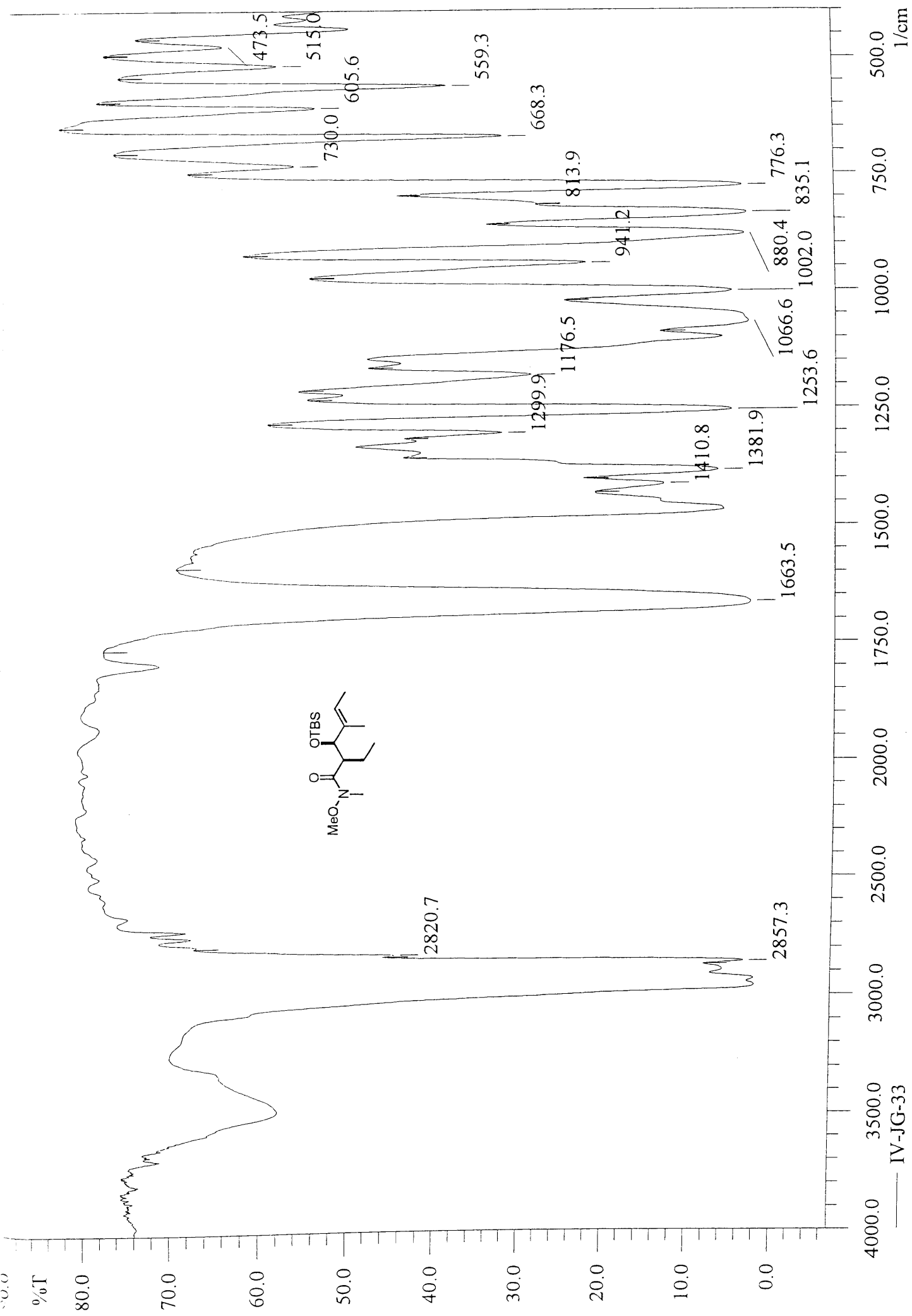


IV-JG-33  
COSY  
CDCl<sub>3</sub>



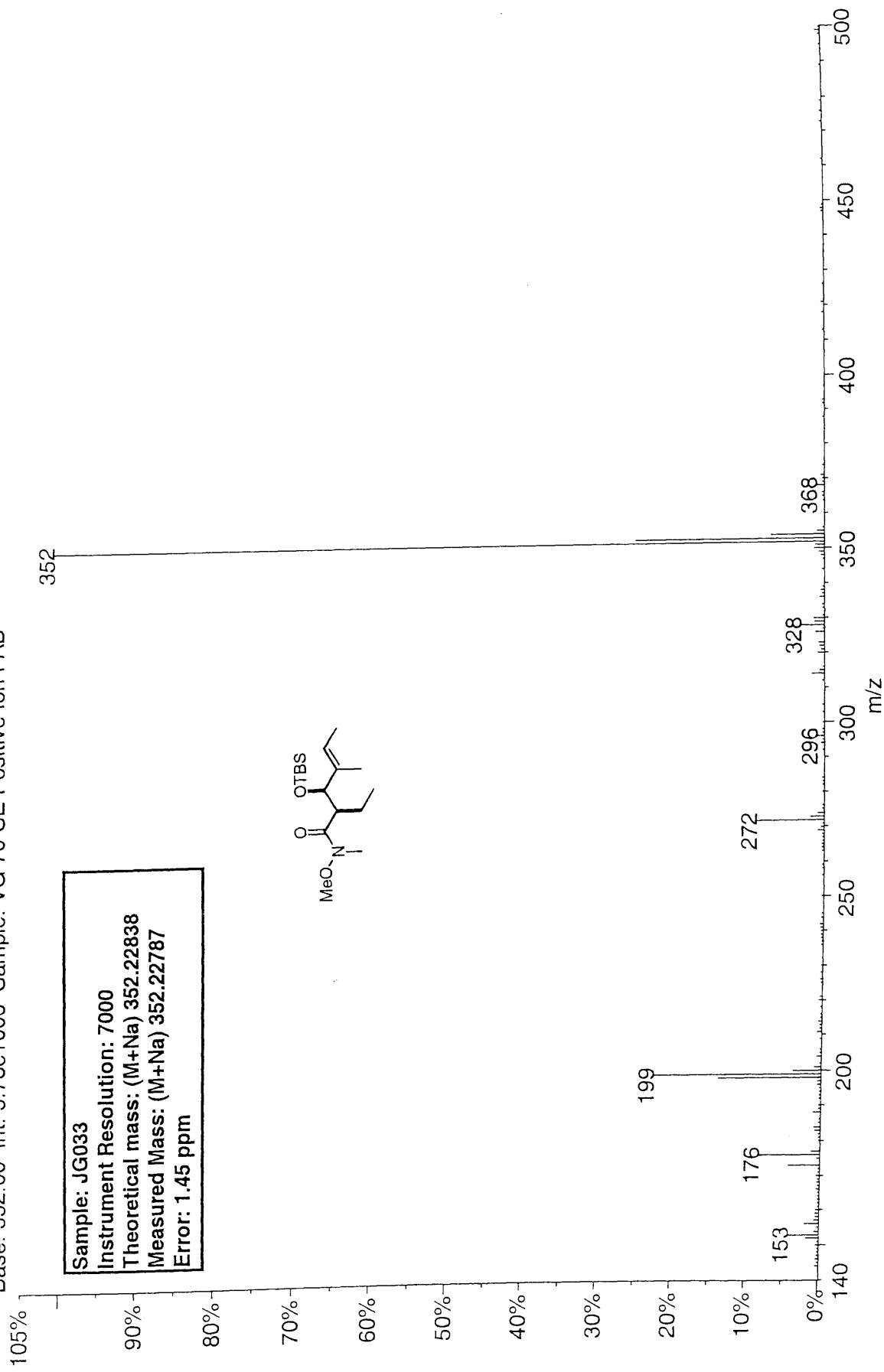
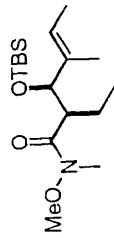
IV-JG-33  
HMQC  
CDCl3





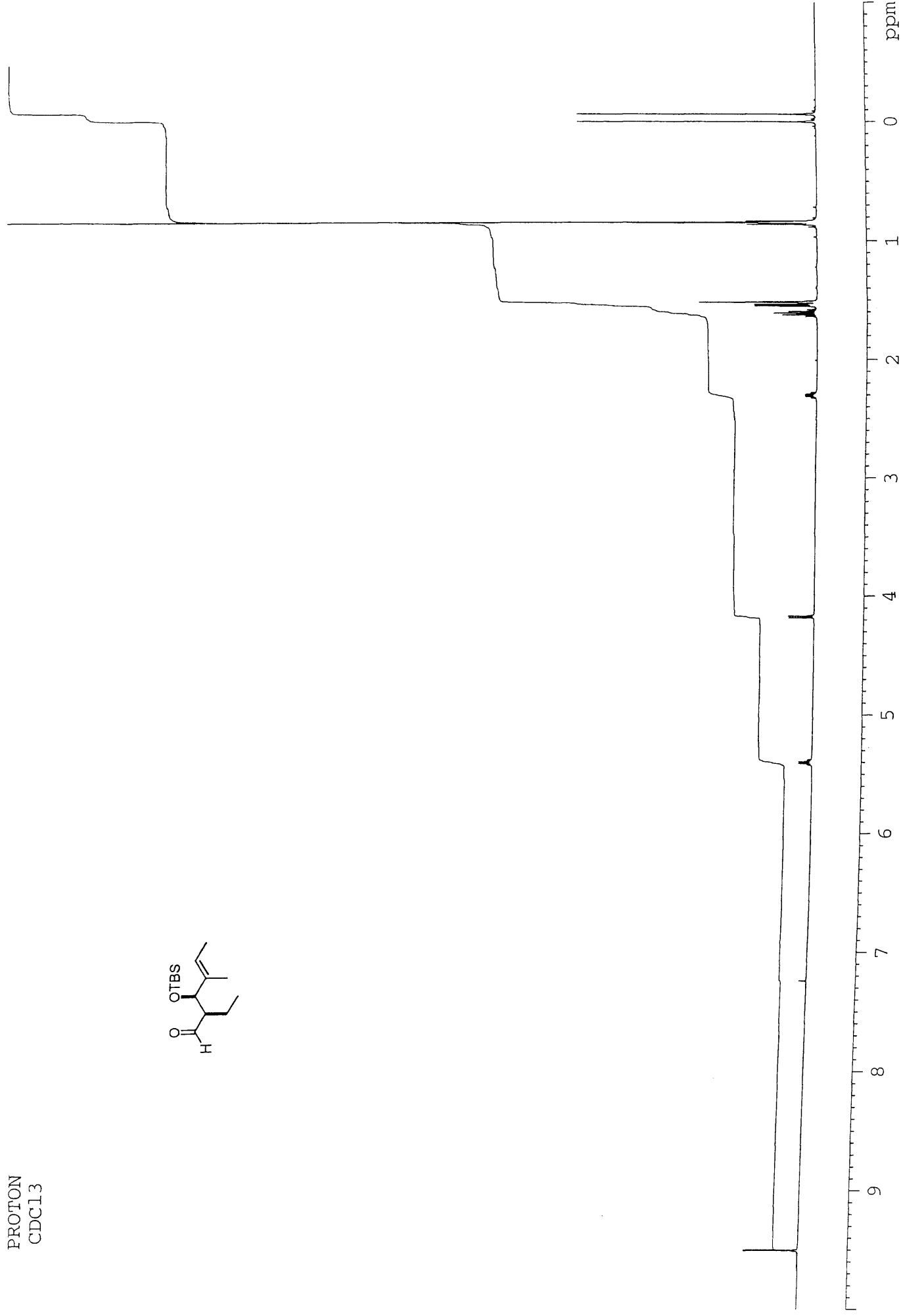
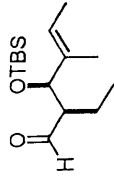
01030406: Scan 78 (14.25 min)  
Base: 352.00 Int: 5.78e+006 Sample: VG 70-SE Positive Ion FAB

Sample: JG033  
Instrument Resolution: 7000  
Theoretical mass: (M+Na) 352.22838  
Measured Mass: (M+Na) 352.22787  
Error: 1.45 ppm

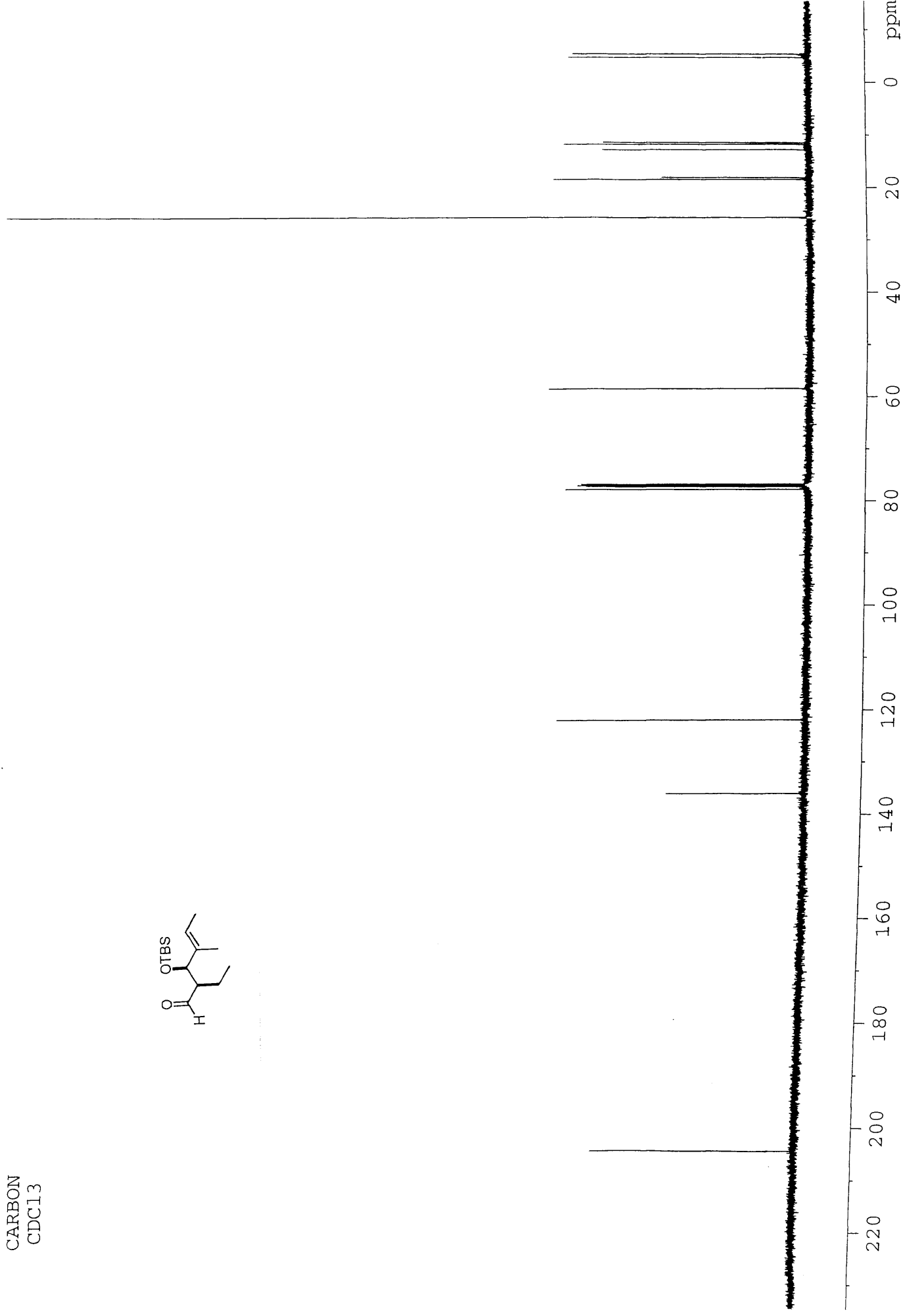
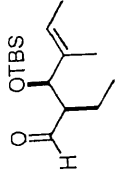


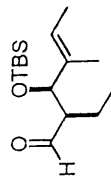


IV-JG--40  
PROTON  
CDCl3

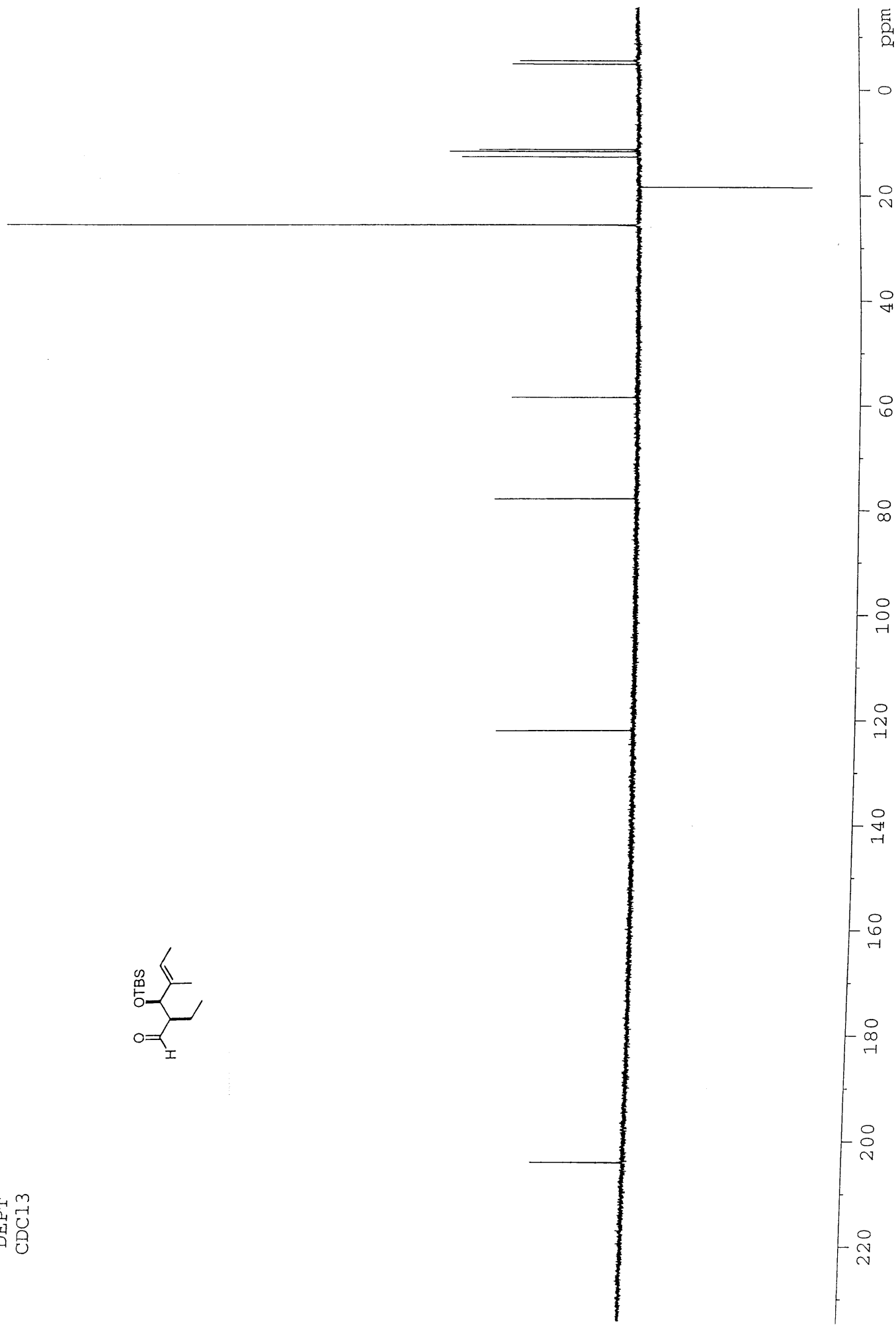


IV-JG-40  
CARBON  
CDCl<sub>3</sub>

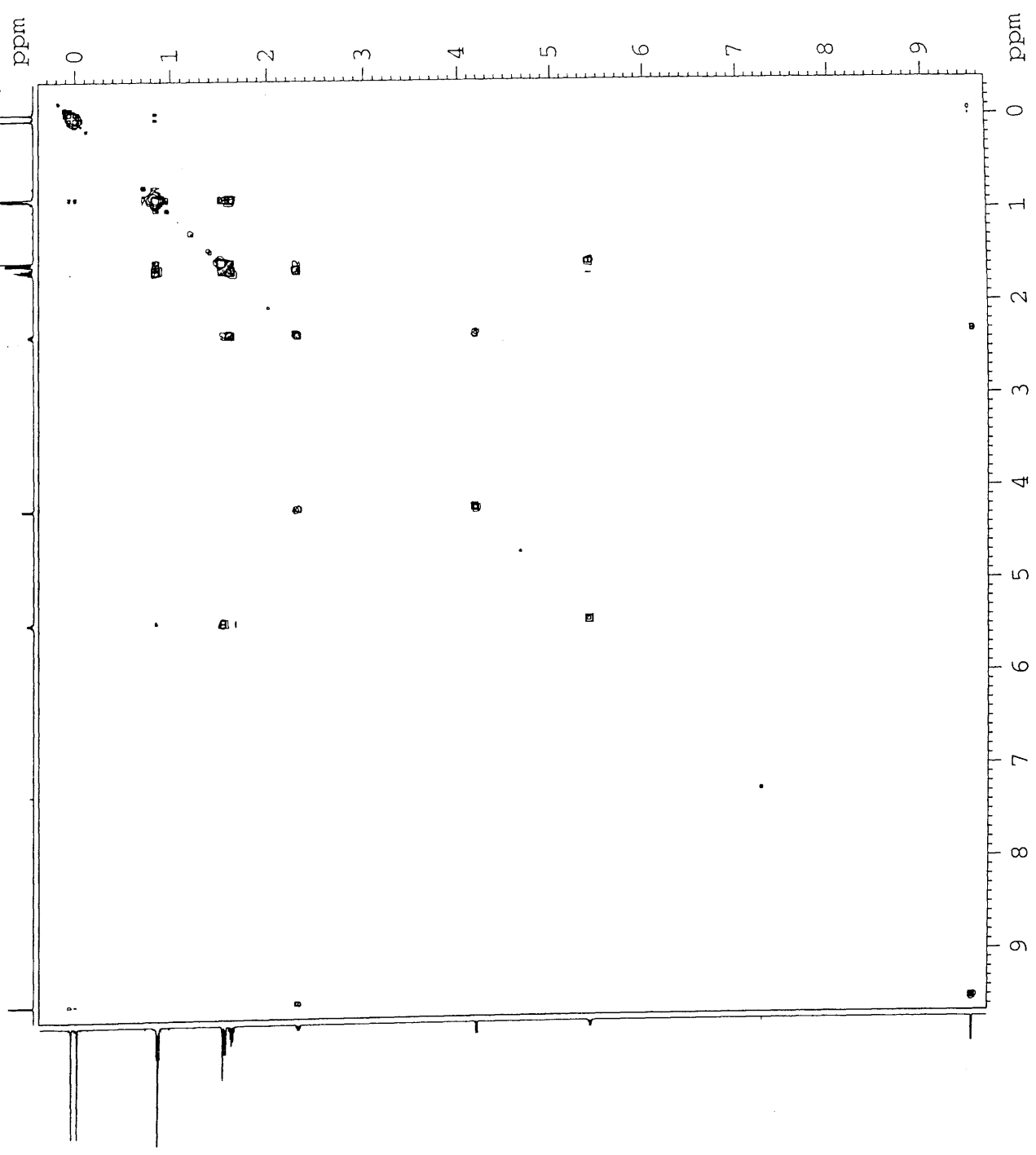
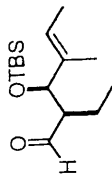


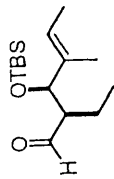


IV-JG-40  
DEPT  
CDCl<sub>3</sub>

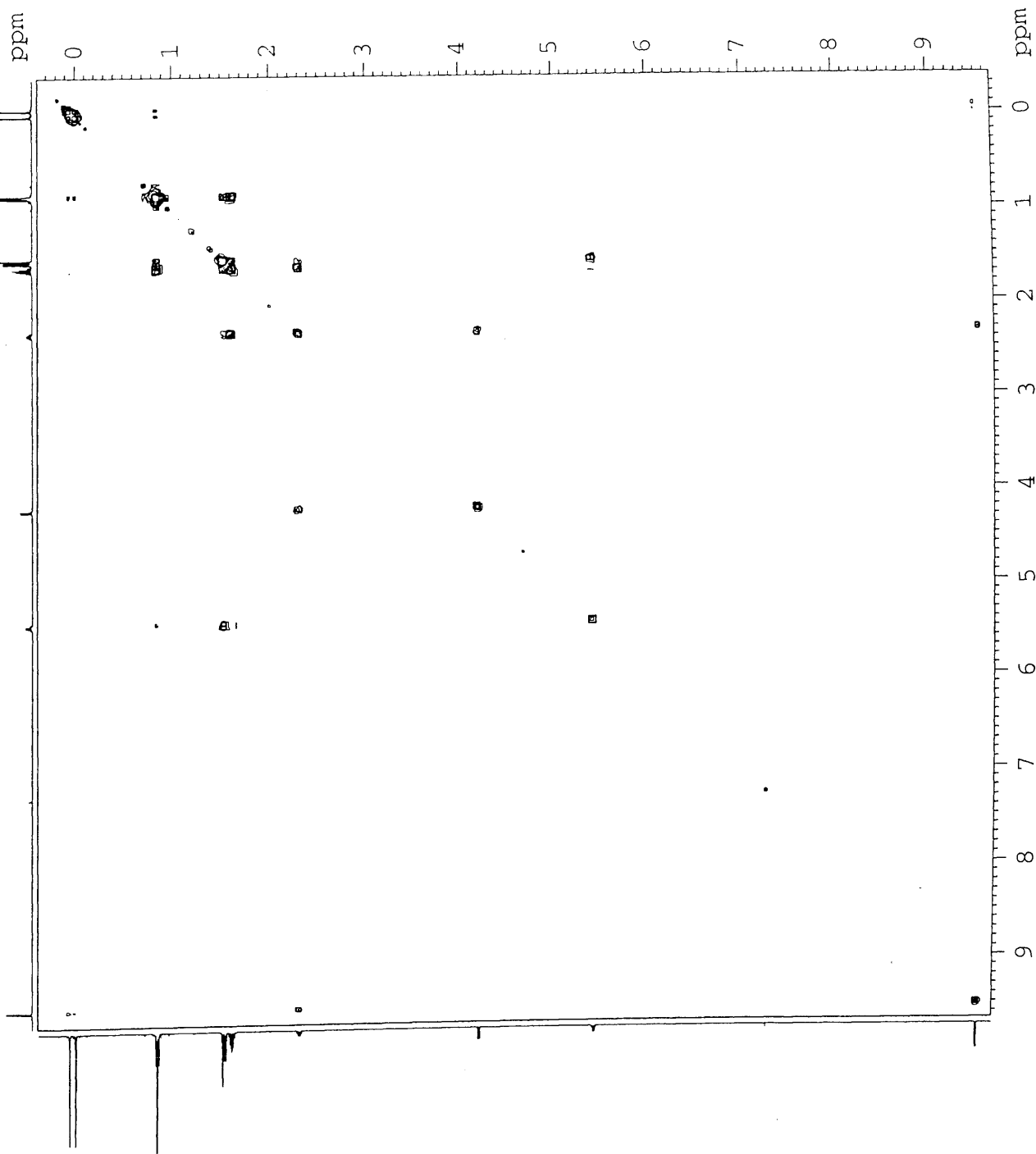


IV-JG-40  
COSY  
CDCl3

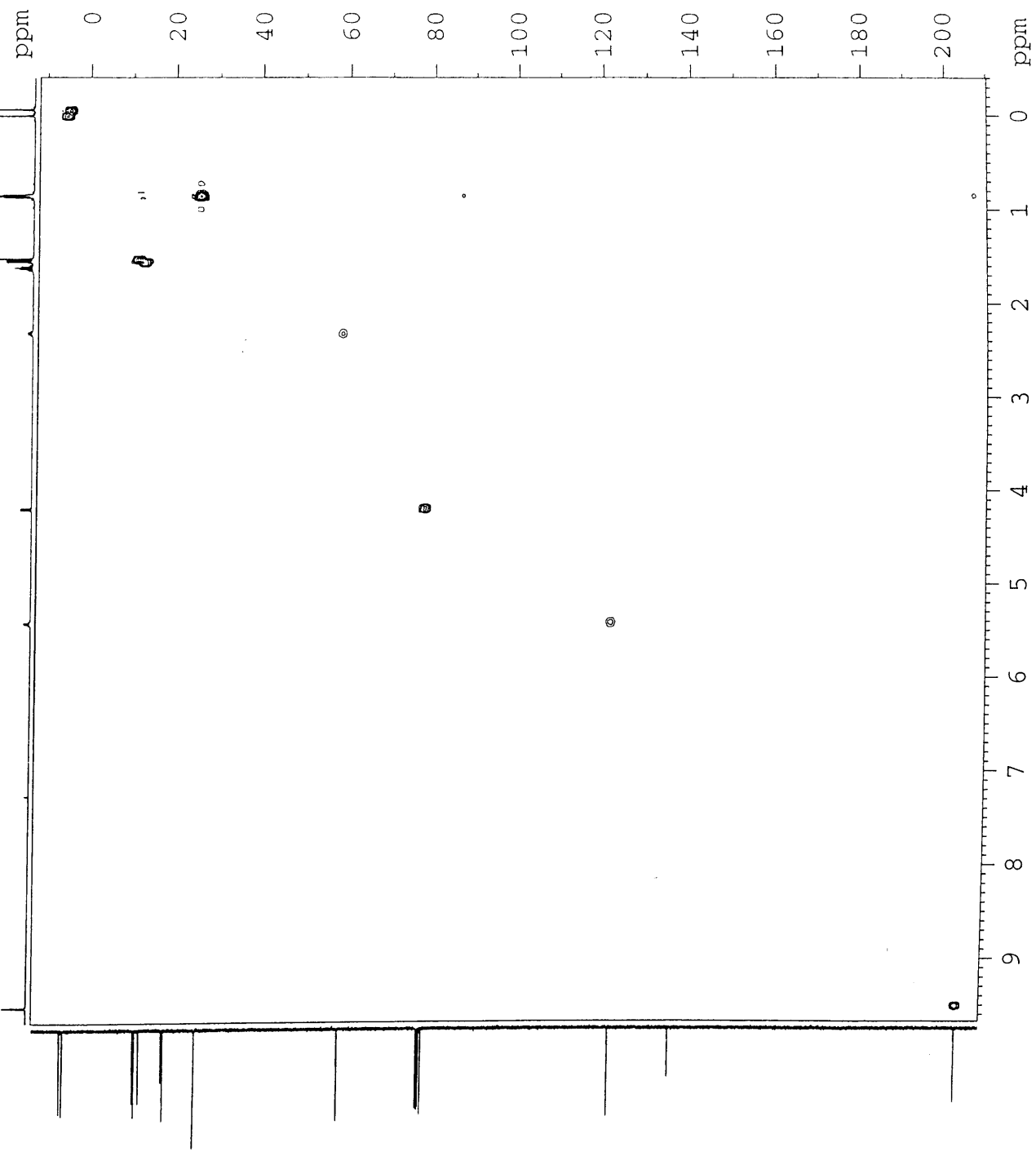
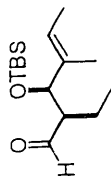


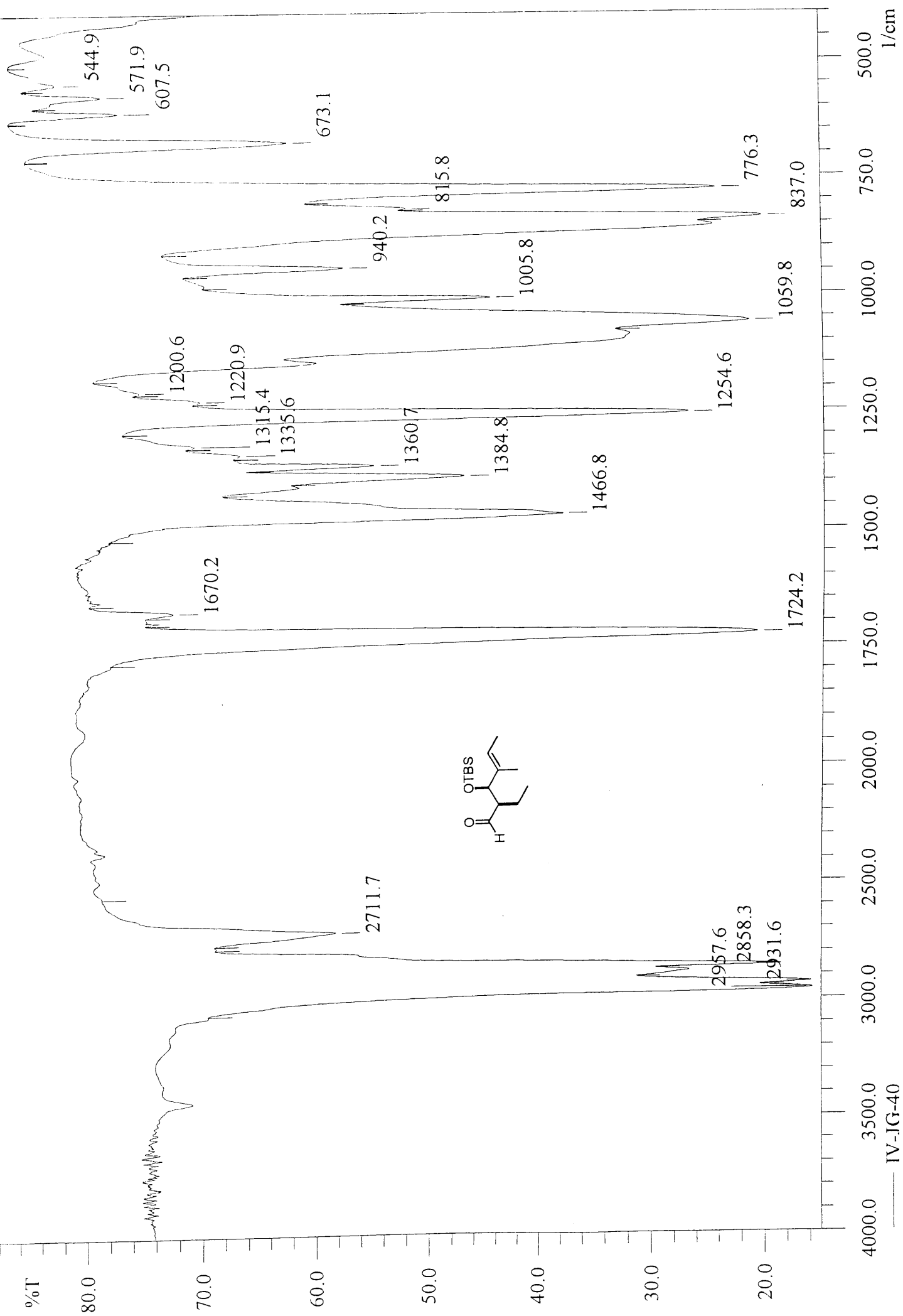


IV-JG-40  
COSY  
CDCl<sub>3</sub>

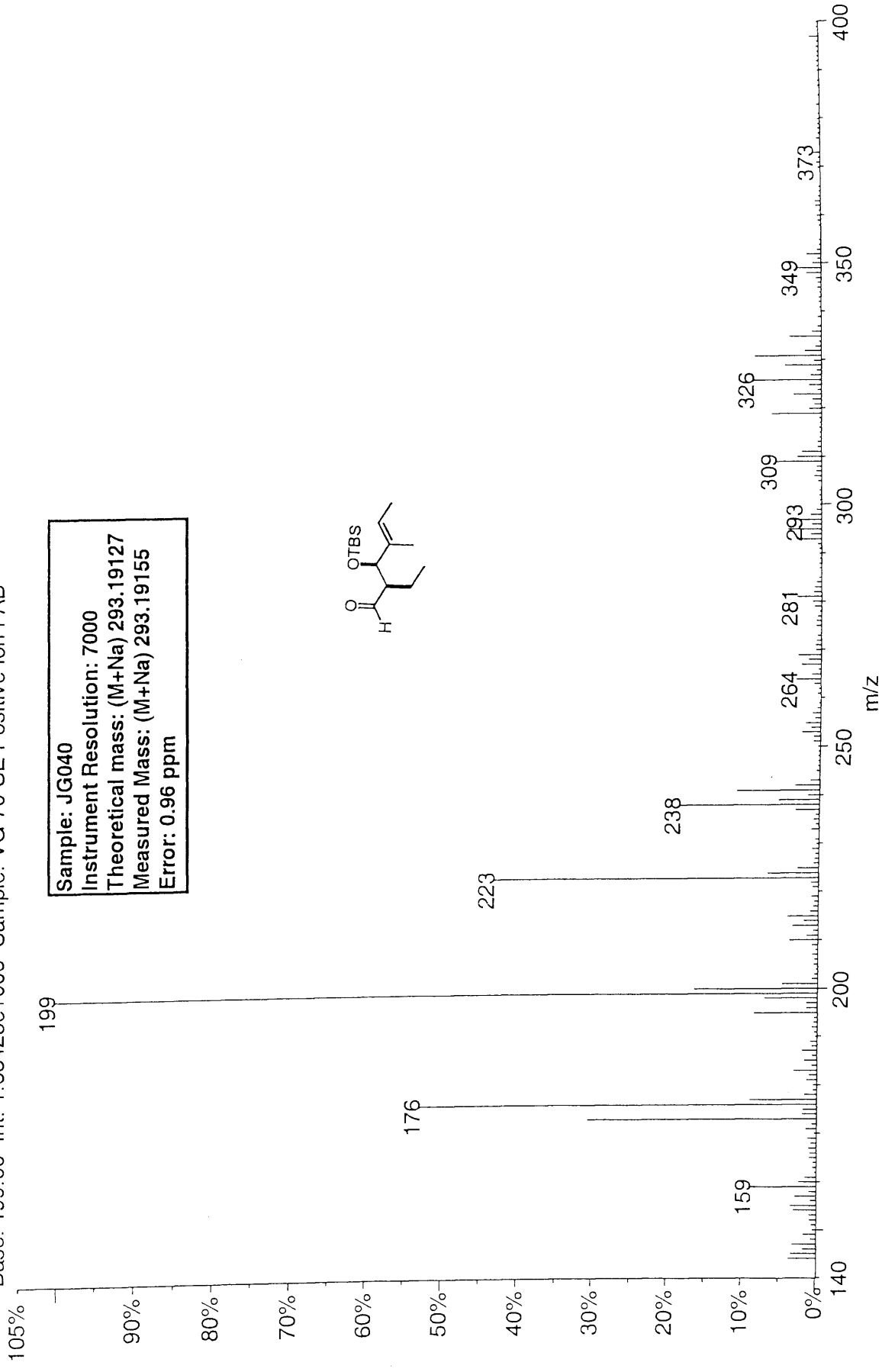


IV-JG-40  
HMQC  
CDCl<sub>3</sub>





01030406: Scan 96 (17.55 min) - Back  
Base: 199.00 Int: 1.68425e+006 Sample: VG 70-SE Positive Ion FAB



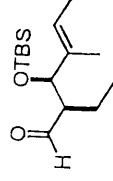
Sample: JG040

Instrument Resolution: 7000

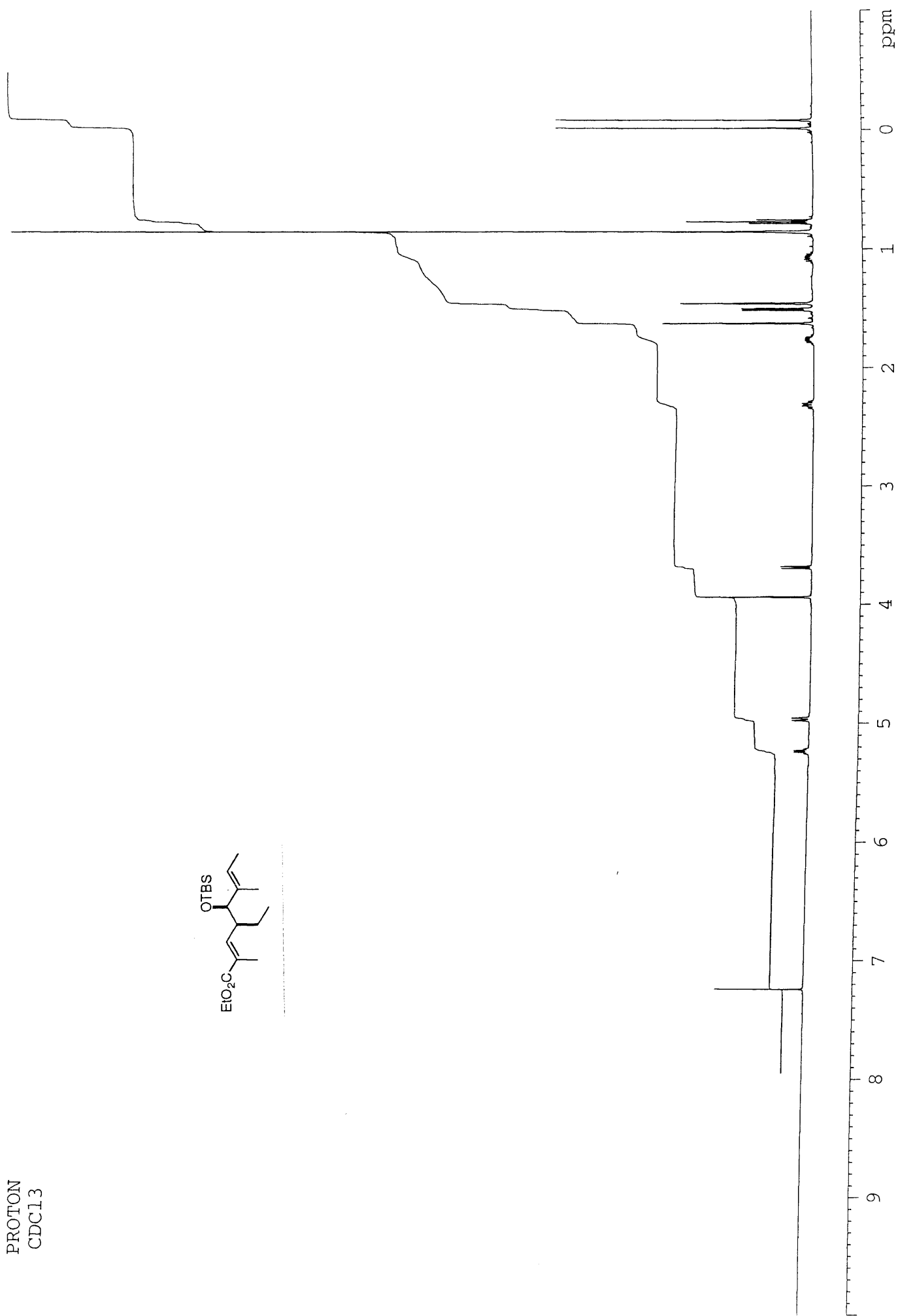
Theoretical mass: (M+Na) 293.19127

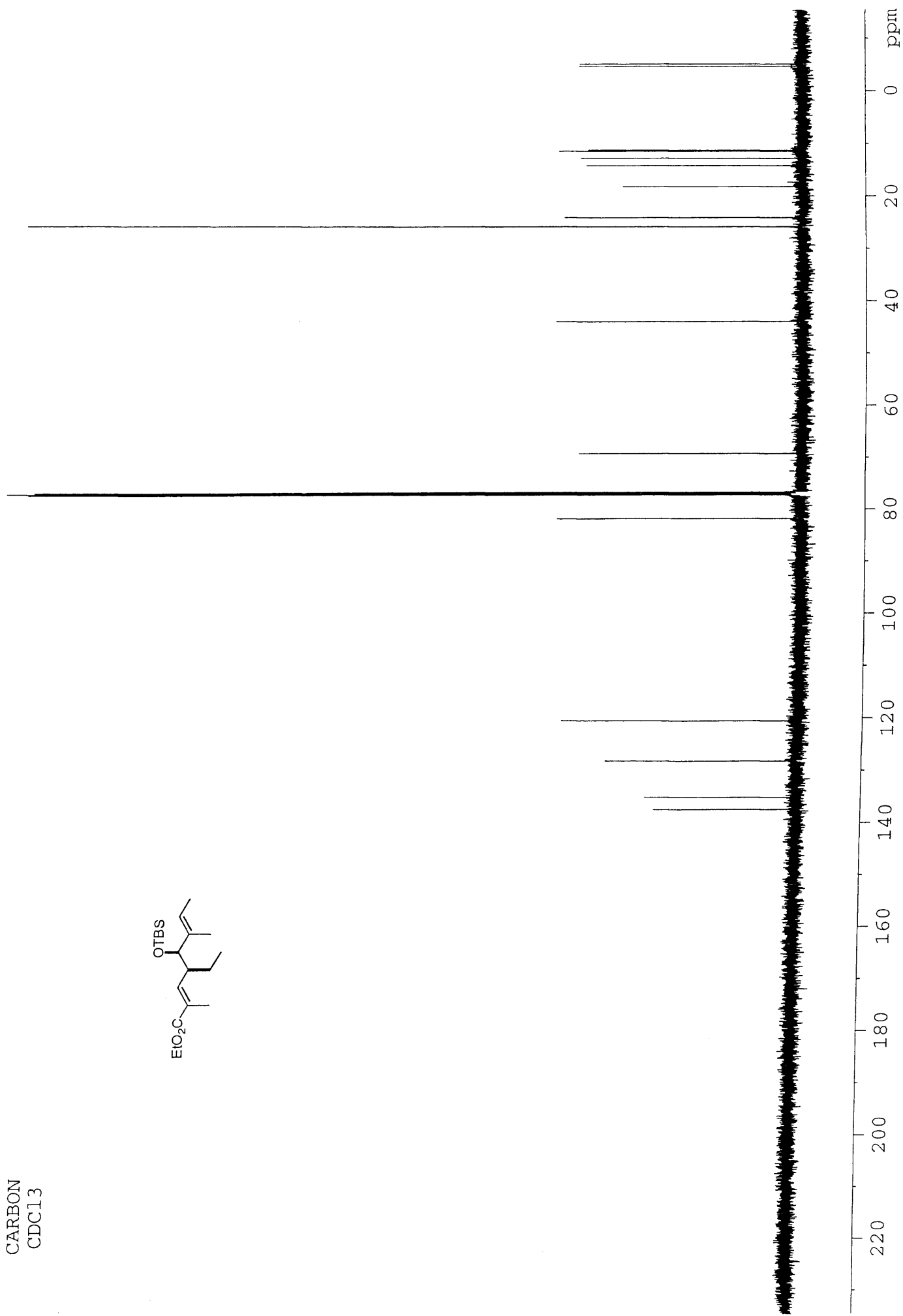
Measured Mass: (M+Na) 293.19155

Error: 0.96 ppm

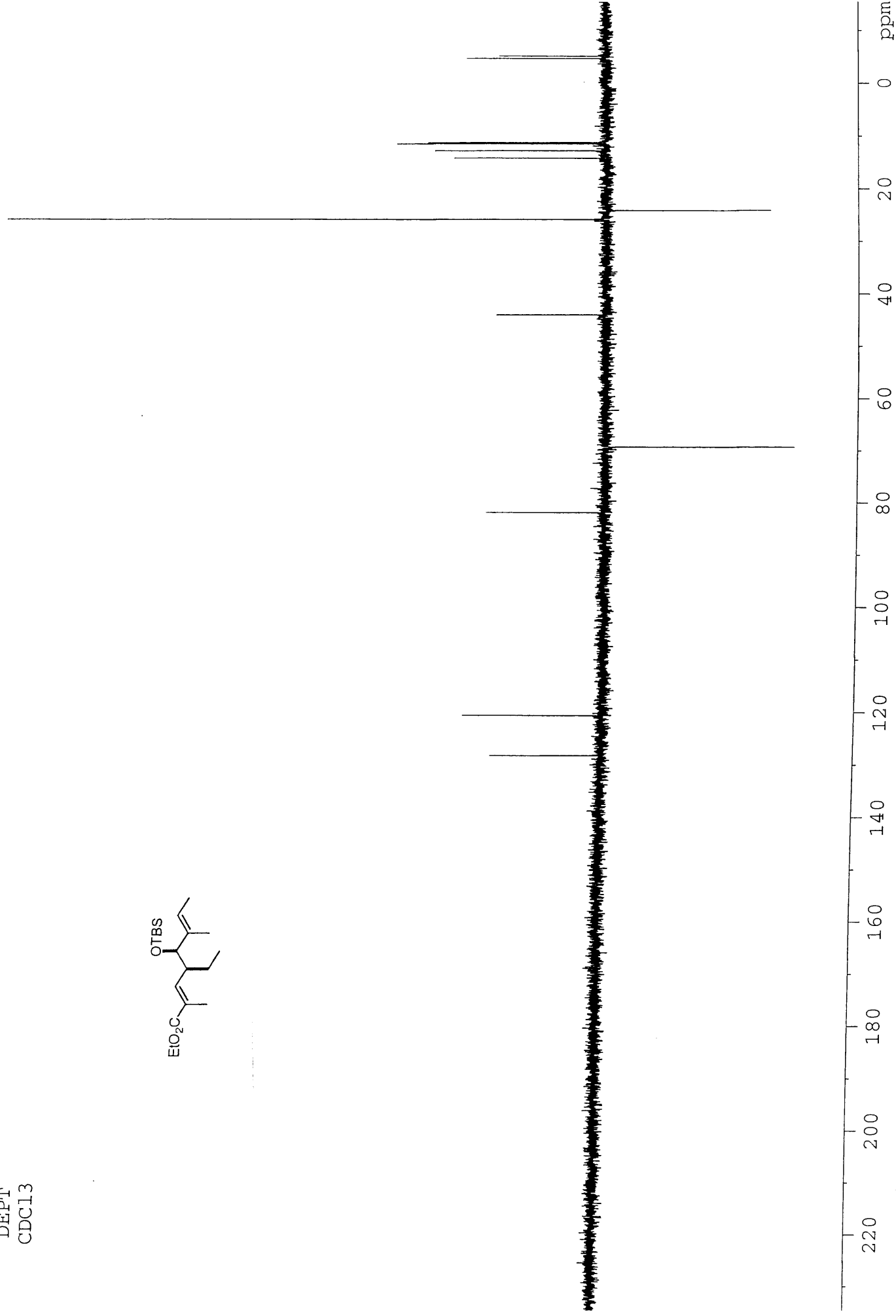
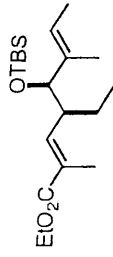




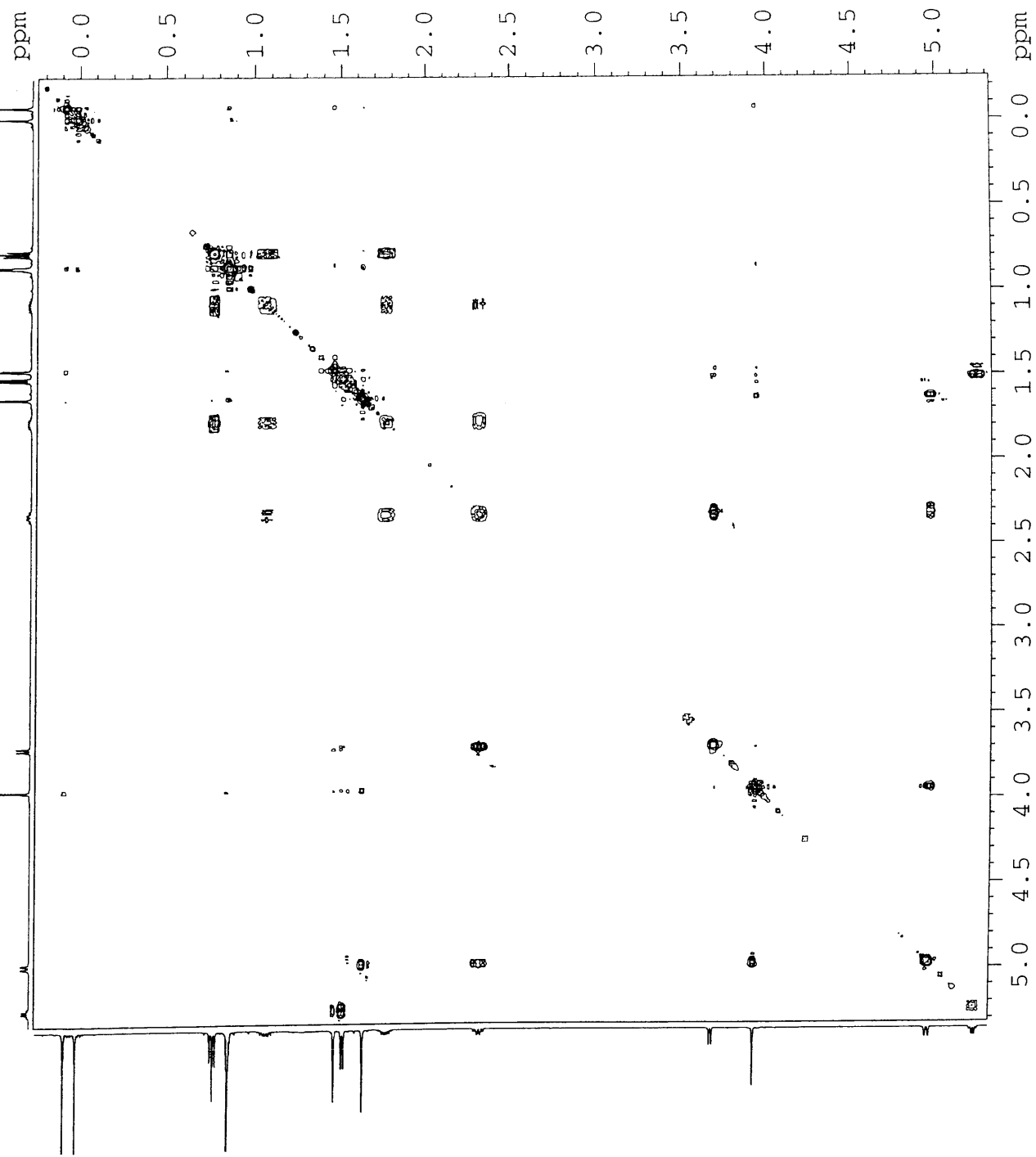
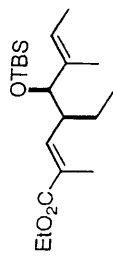
CC(C)=CC(C)(C)C(=C)C(C)C(C)C(=O)O[Si](C)(C)C

CC(C)=CC(=C)C(C)C(=O)OCC

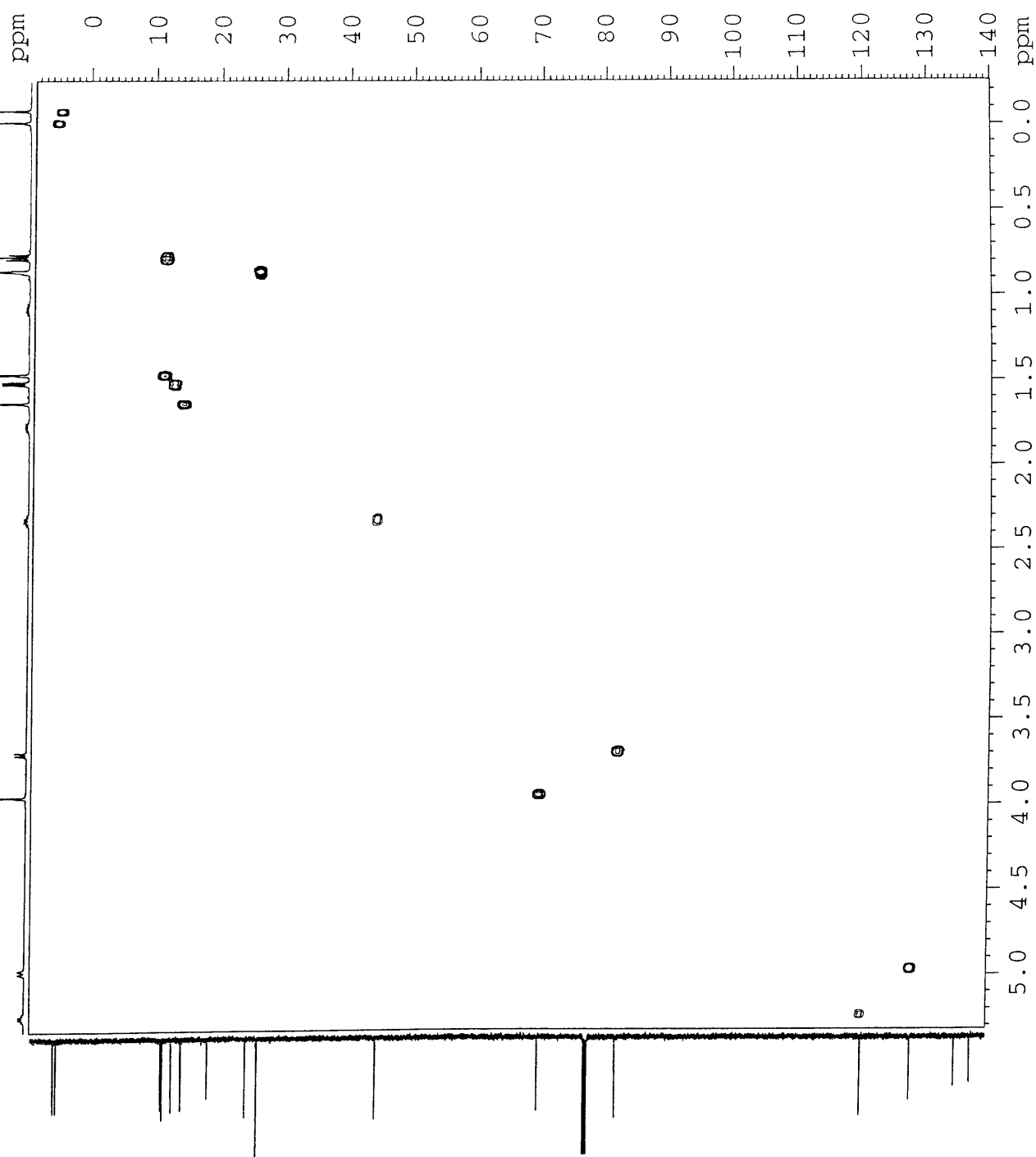
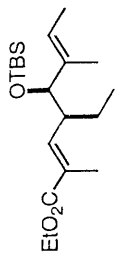
IV-JG-43  
DEPT  
CDCl<sub>3</sub>

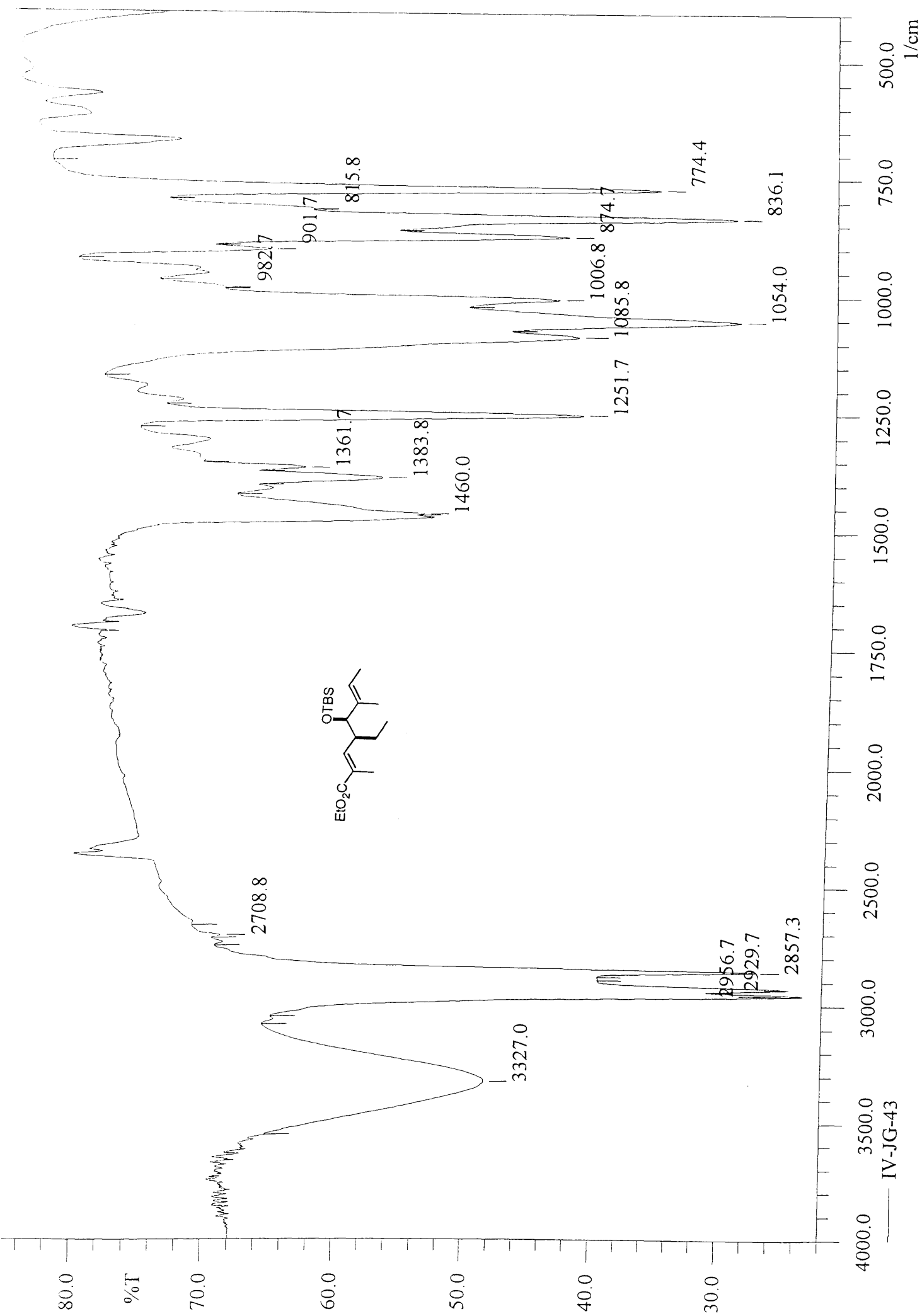


IV-JG-43  
COSY  
CDCl<sub>3</sub>



IV-JG-43  
HMQC  
CDCl<sub>3</sub>





02110506: Scan 72 (13.15 min) - Back  
Base: 199.00 Int: 2.77055e+006 Sample: VG 70-SE Positive Ion FAB

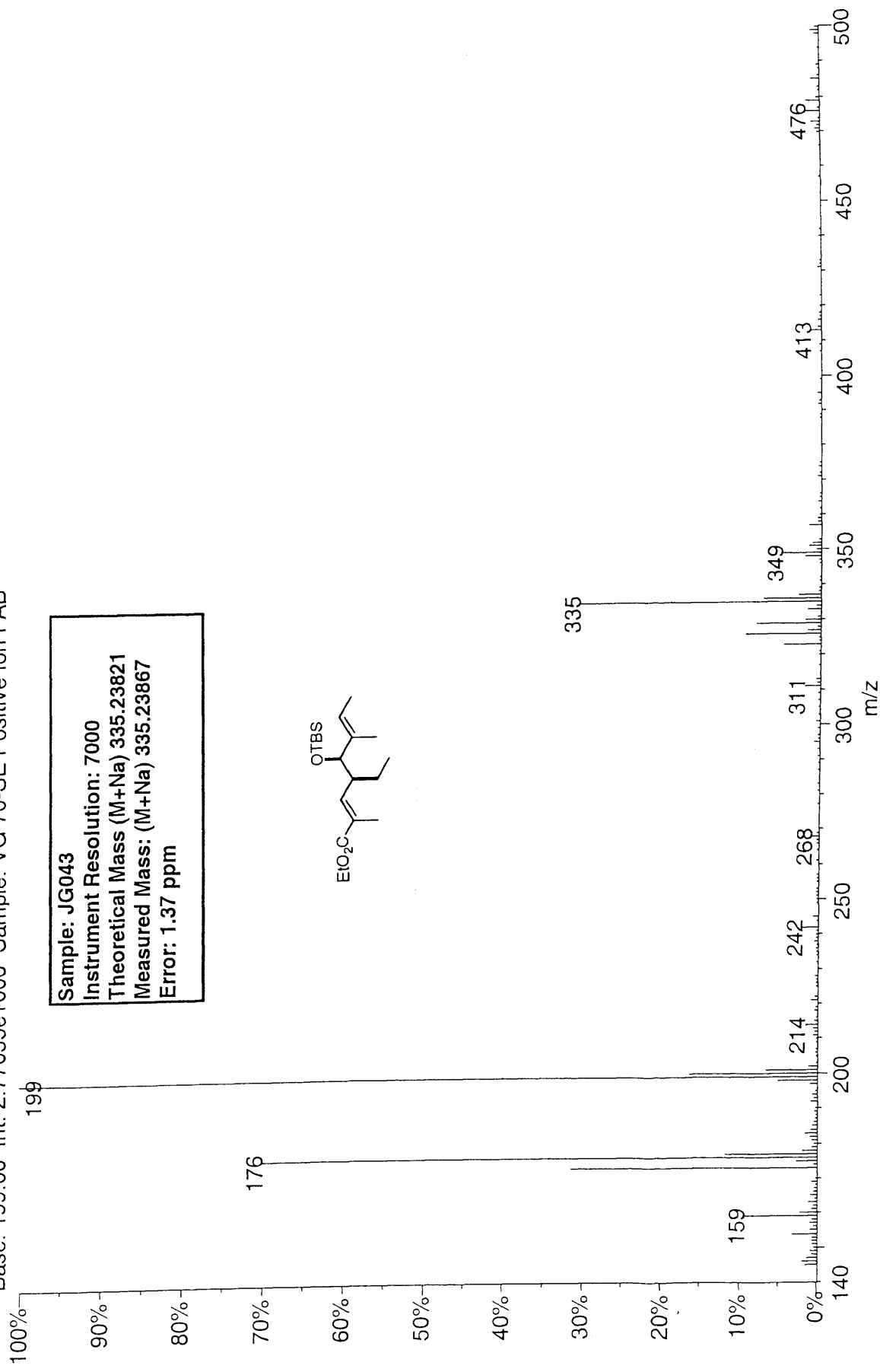
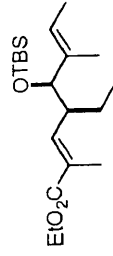
Sample: JG043

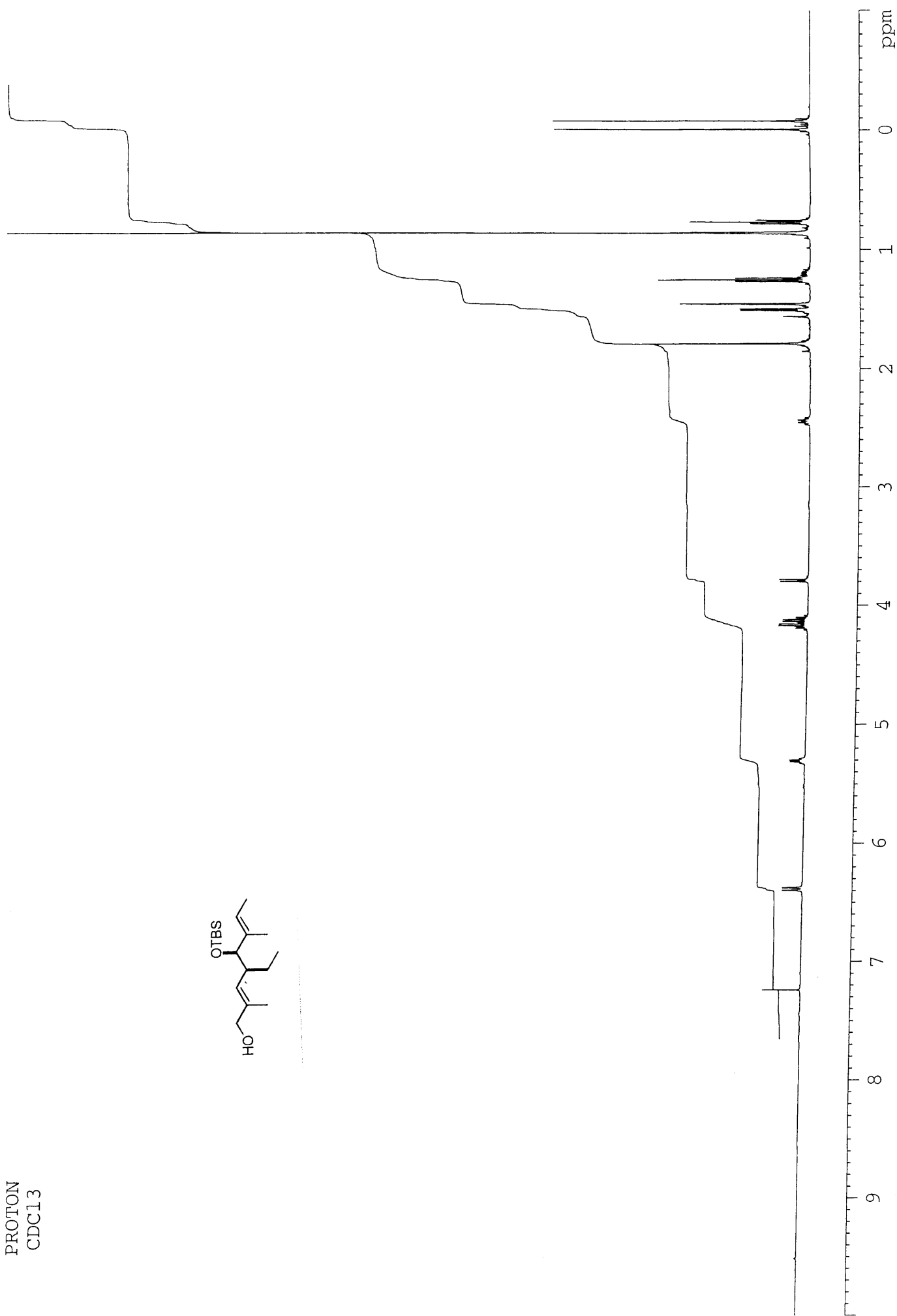
Instrument Resolution: 7000

Theoretical Mass (M+Na) 335.23821

Measured Mass: (M+Na) 335.23867

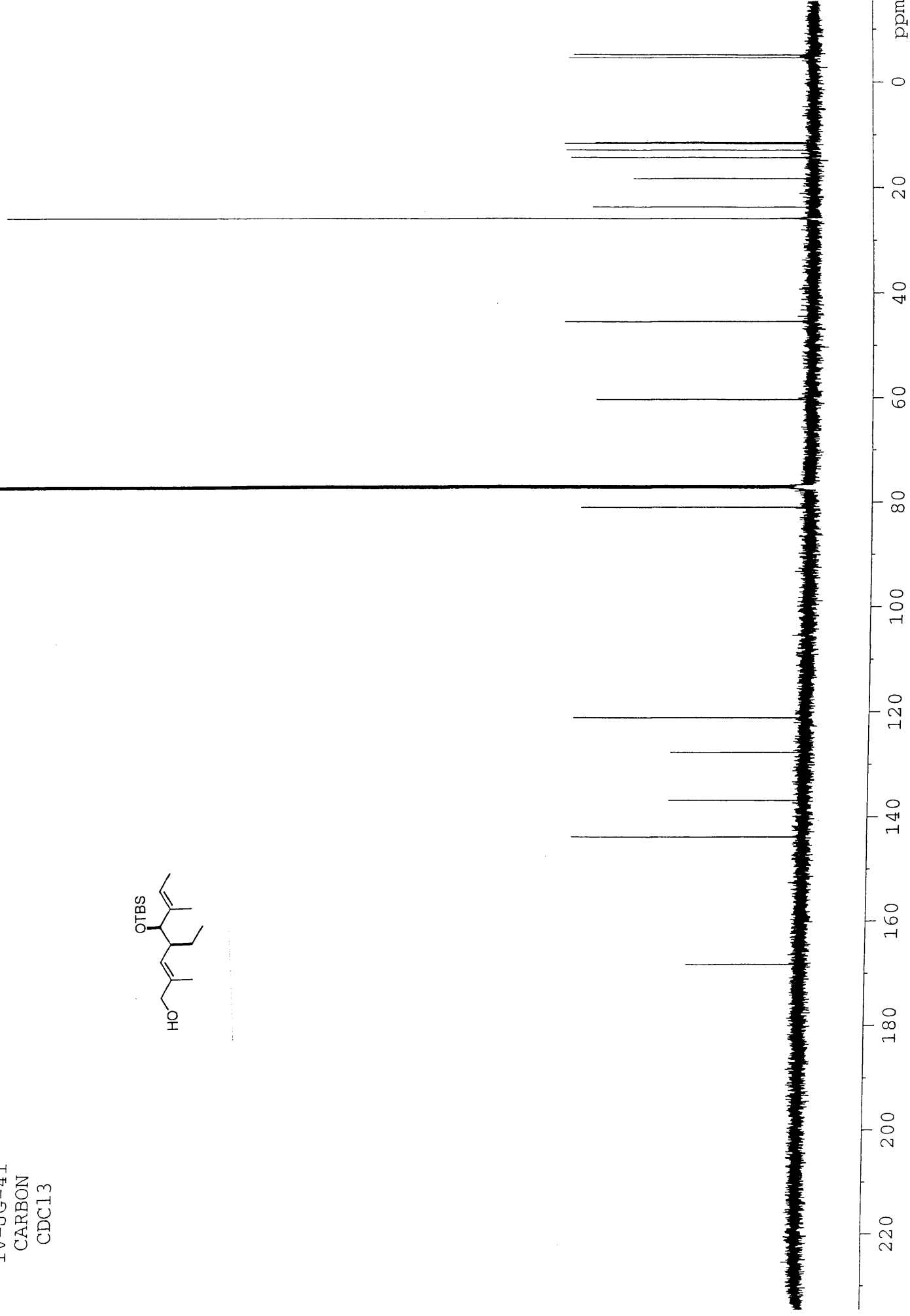
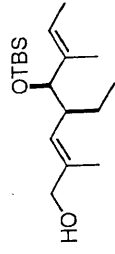
Error: 1.37 ppm



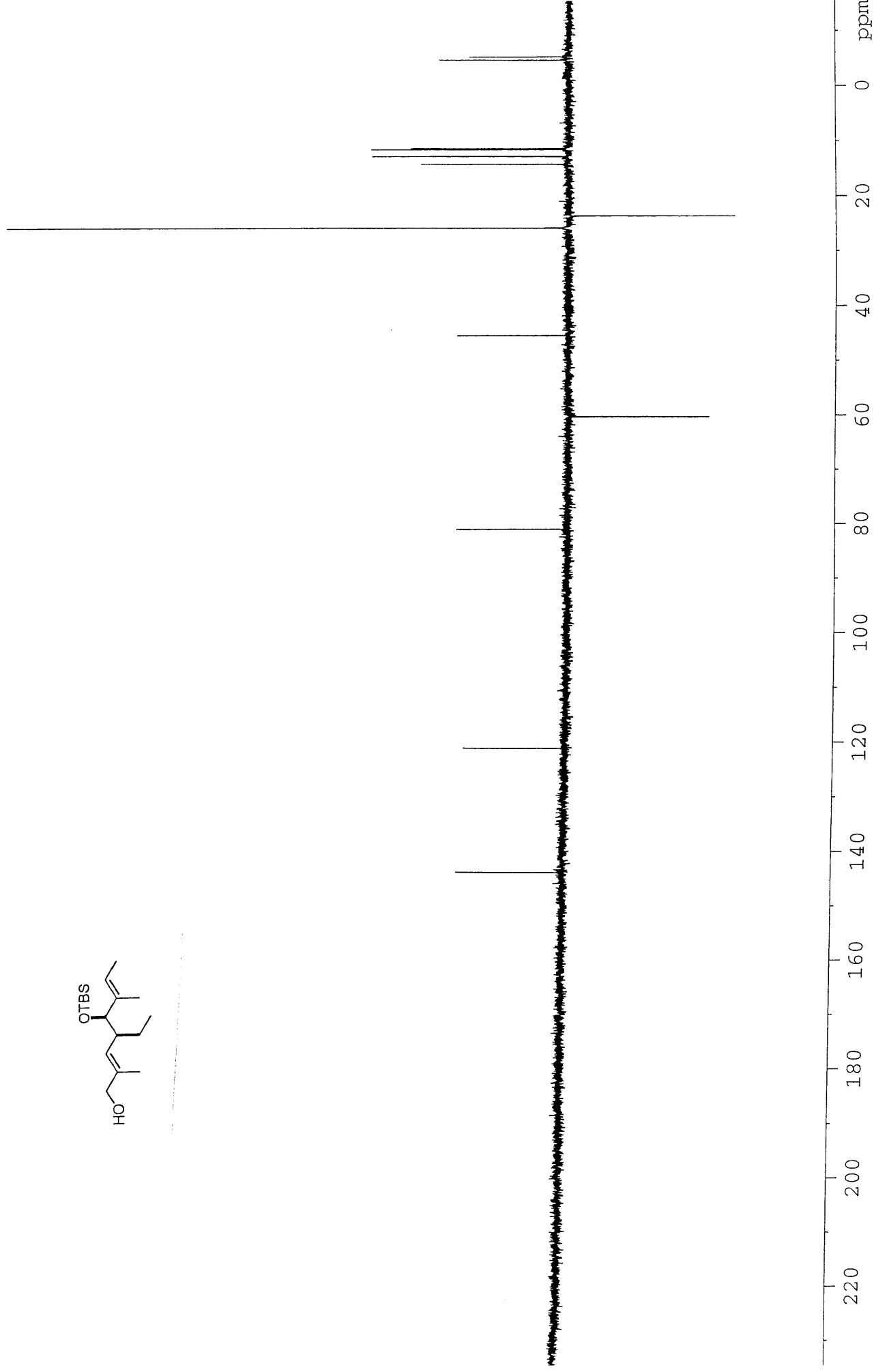
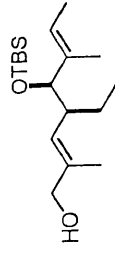
C[C@H](C)[C@@H](O)C=C(C)[C@H](C)OSi(C)(C)C



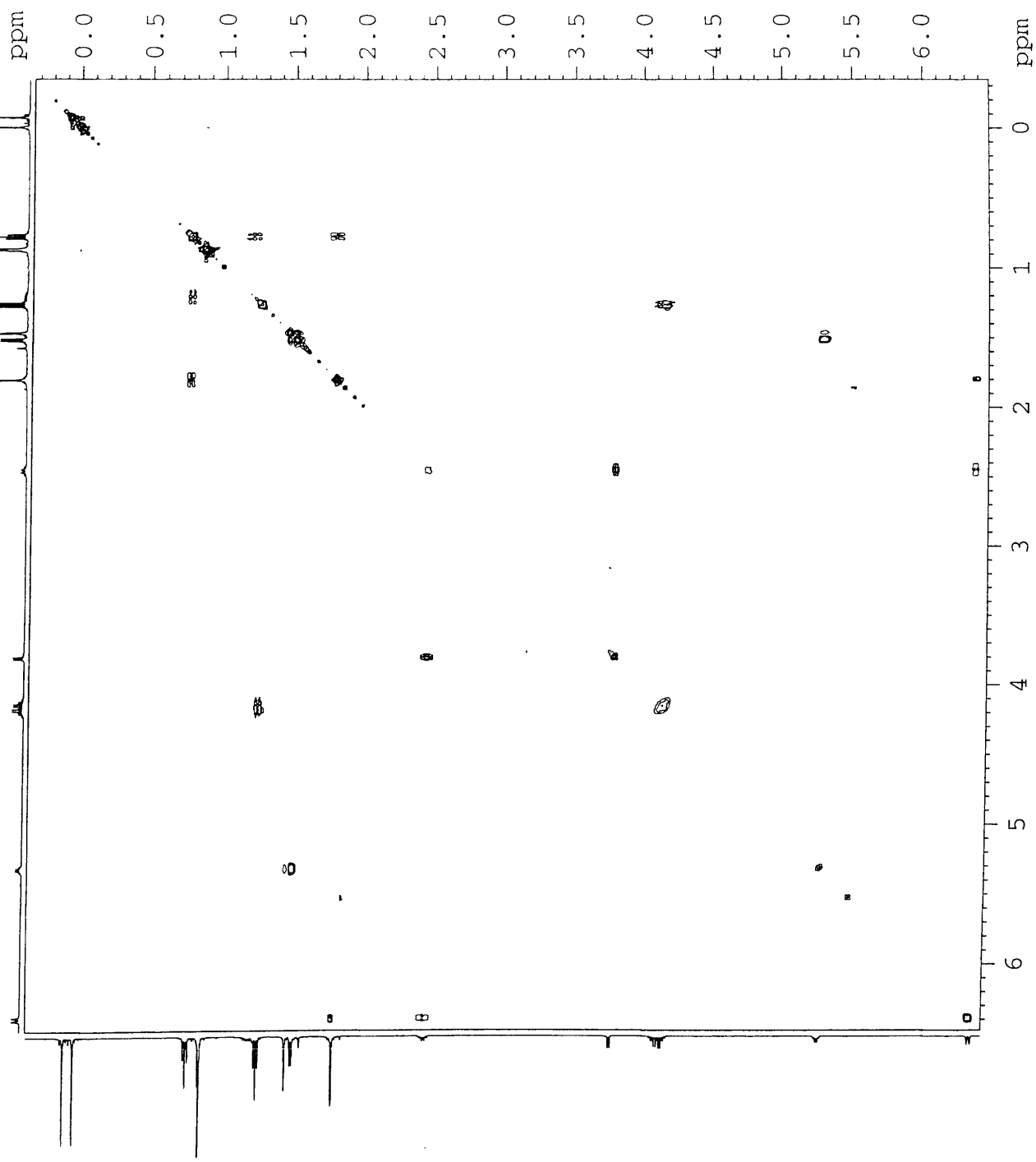
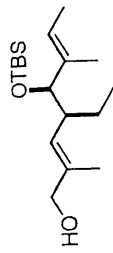
IV-JG-41  
CARBON  
CDCl3

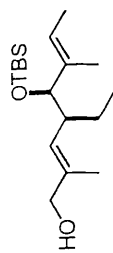


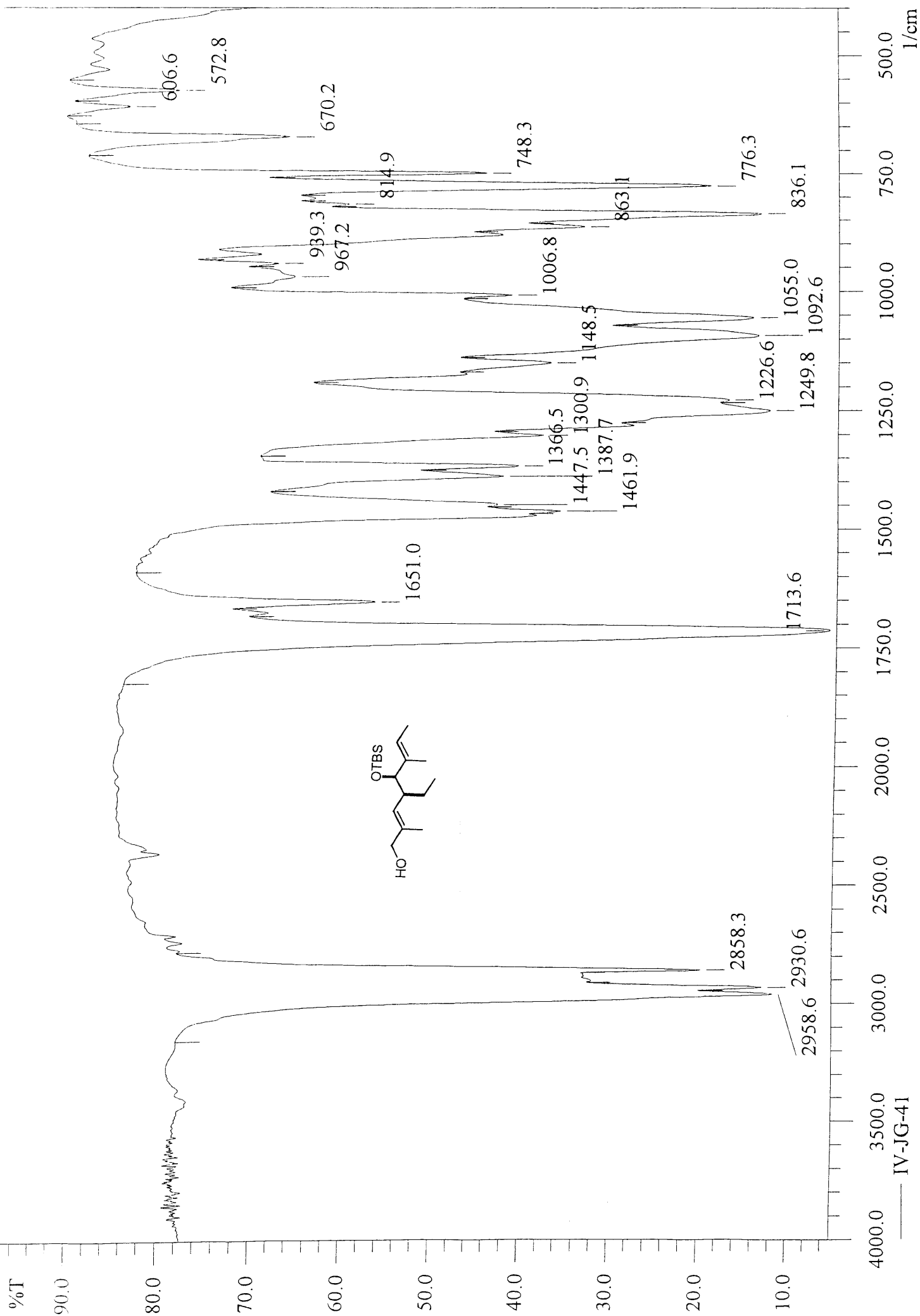
IV-JG-41  
DEPT  
CDC13



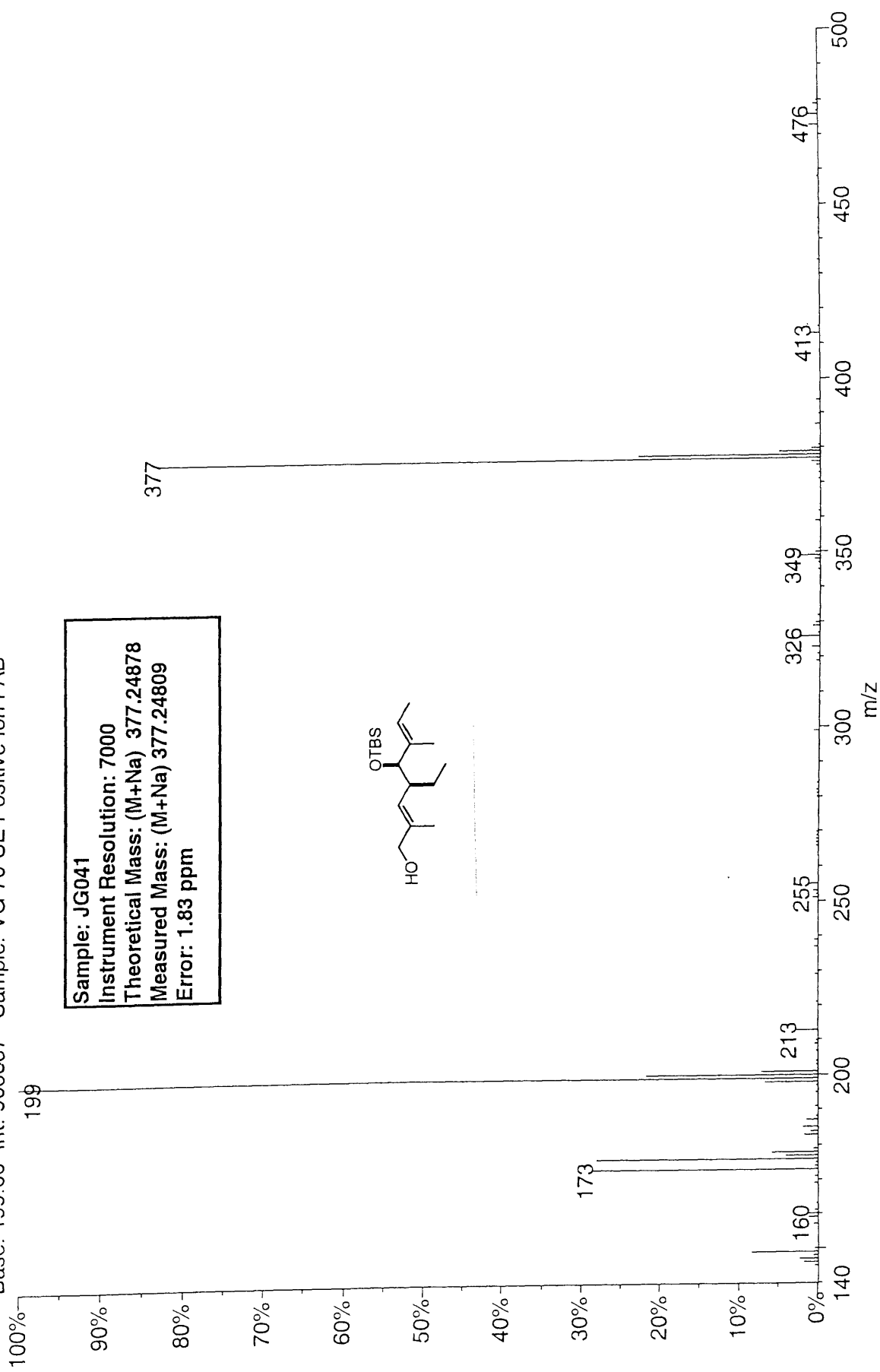
IV-JG-41  
COSY  
CDCl<sub>3</sub>



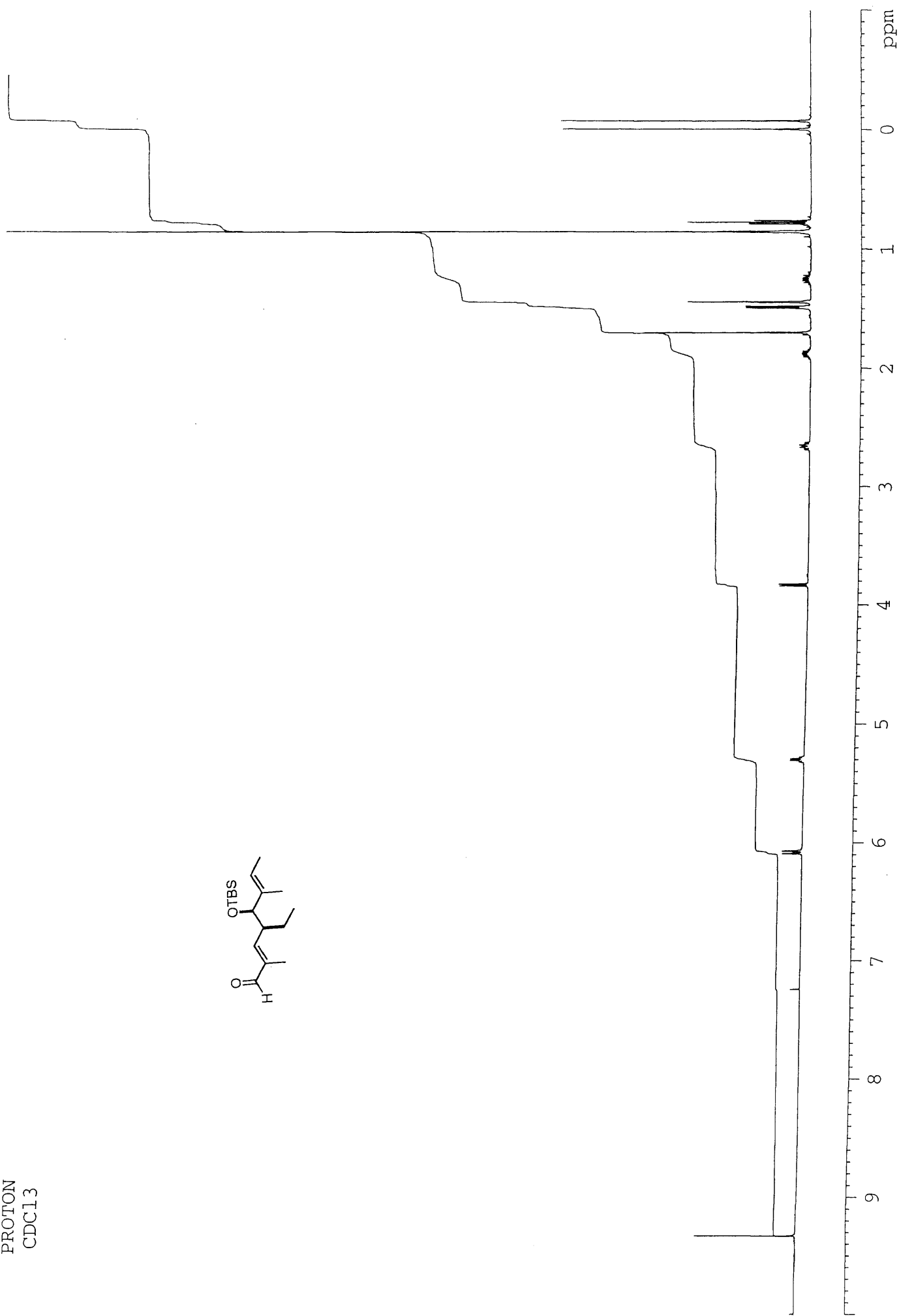
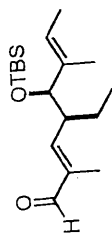




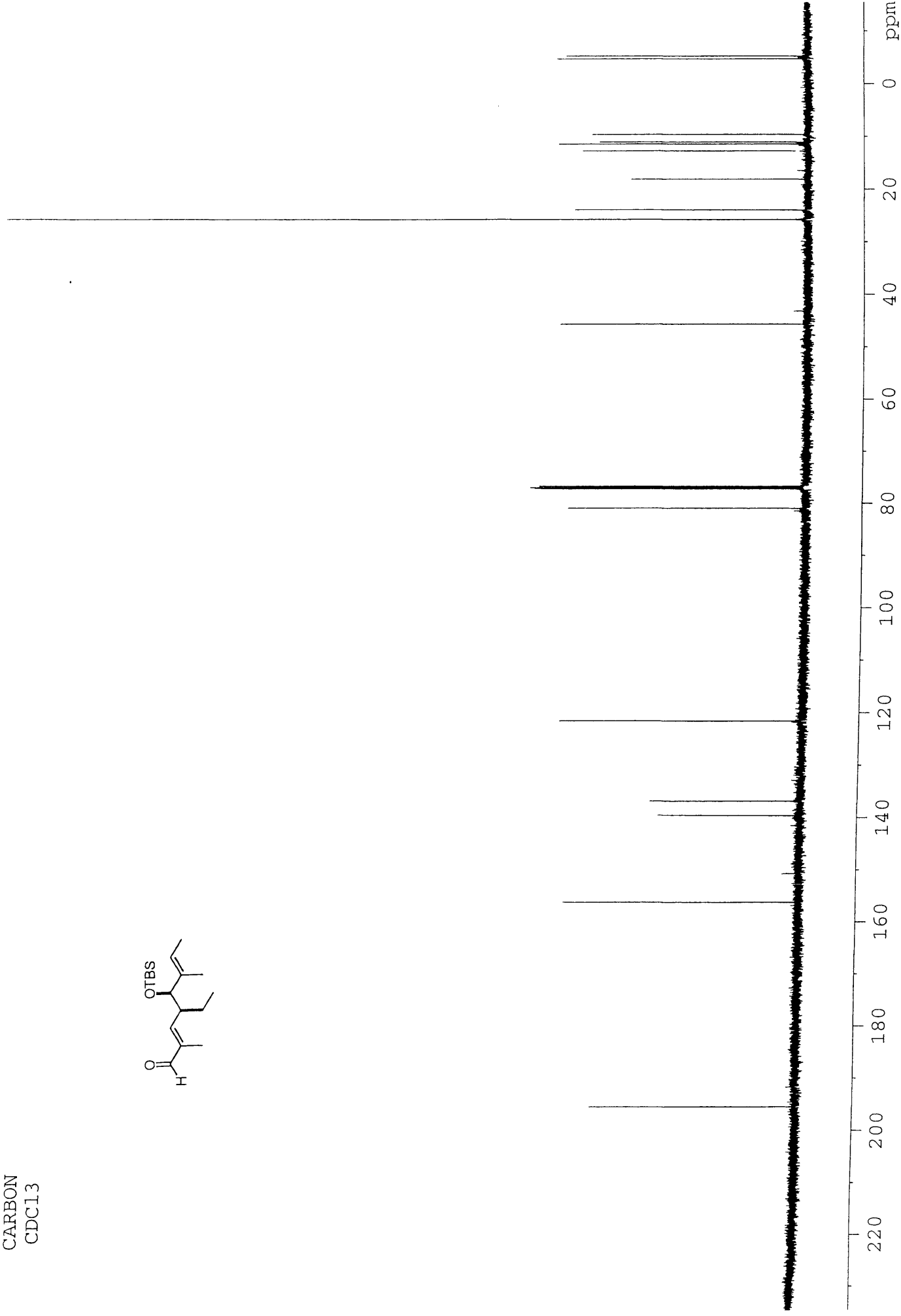
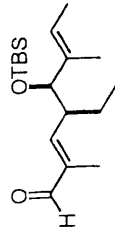
01250506: Scan 32 (5.82 min) - Back  
Base: 199.00 Int: 903837 Sample: VG 70-SE Positive Ion FAB



IV-JG-55  
PROTON  
CDCl<sub>3</sub>

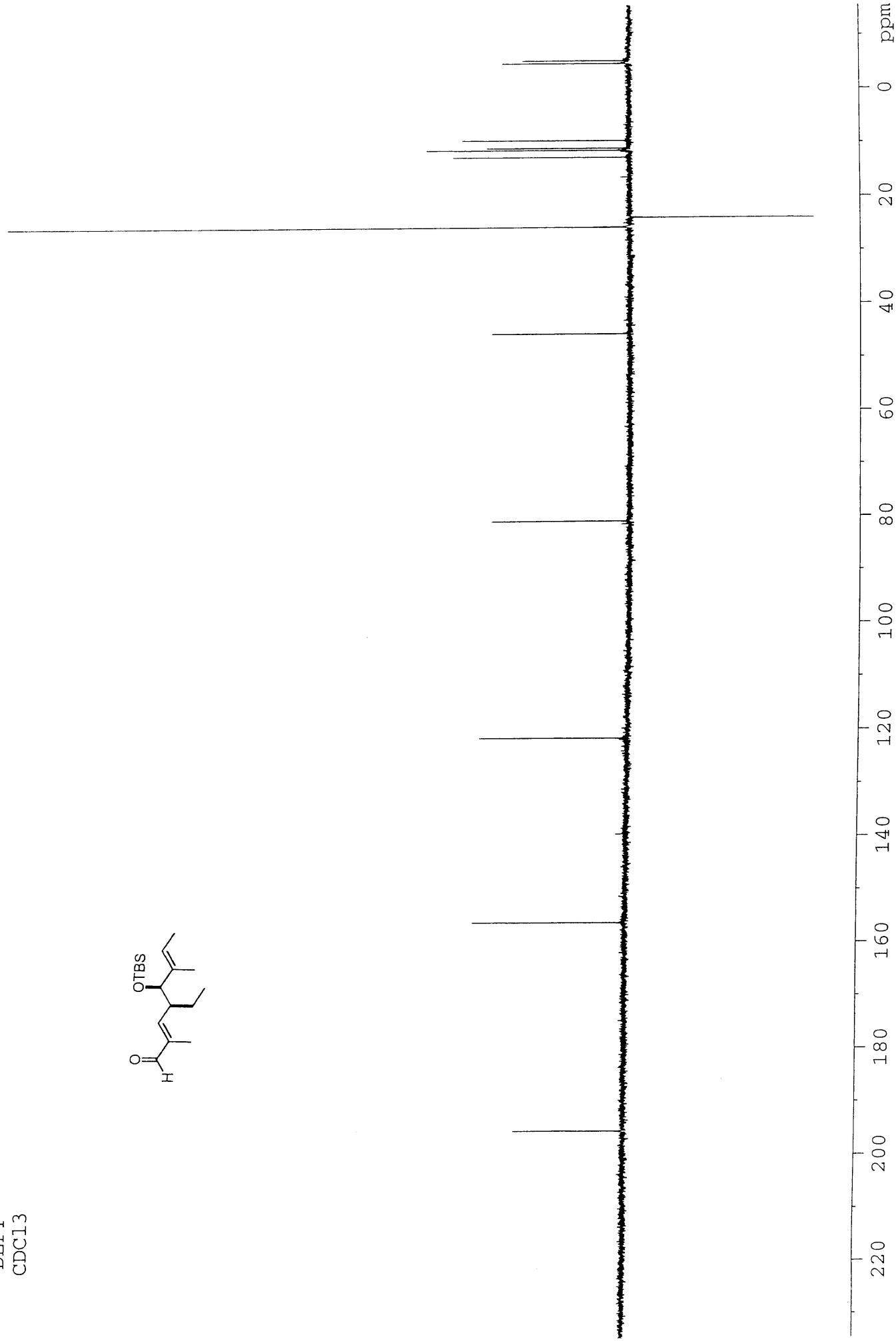
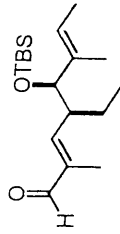


IV-JG-55  
CARBON  
CDCl<sub>3</sub>

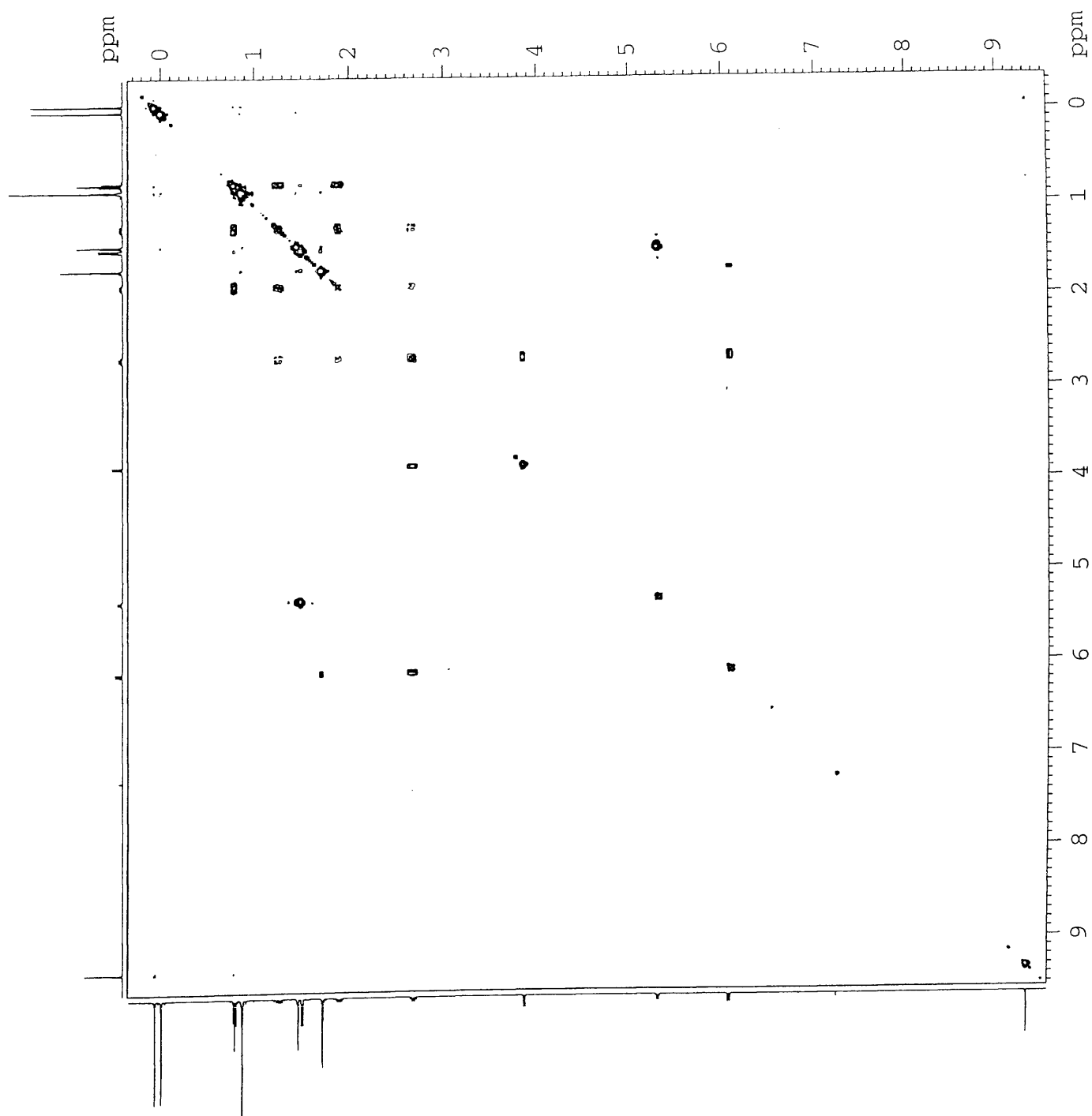
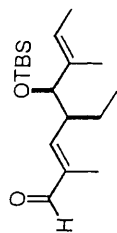


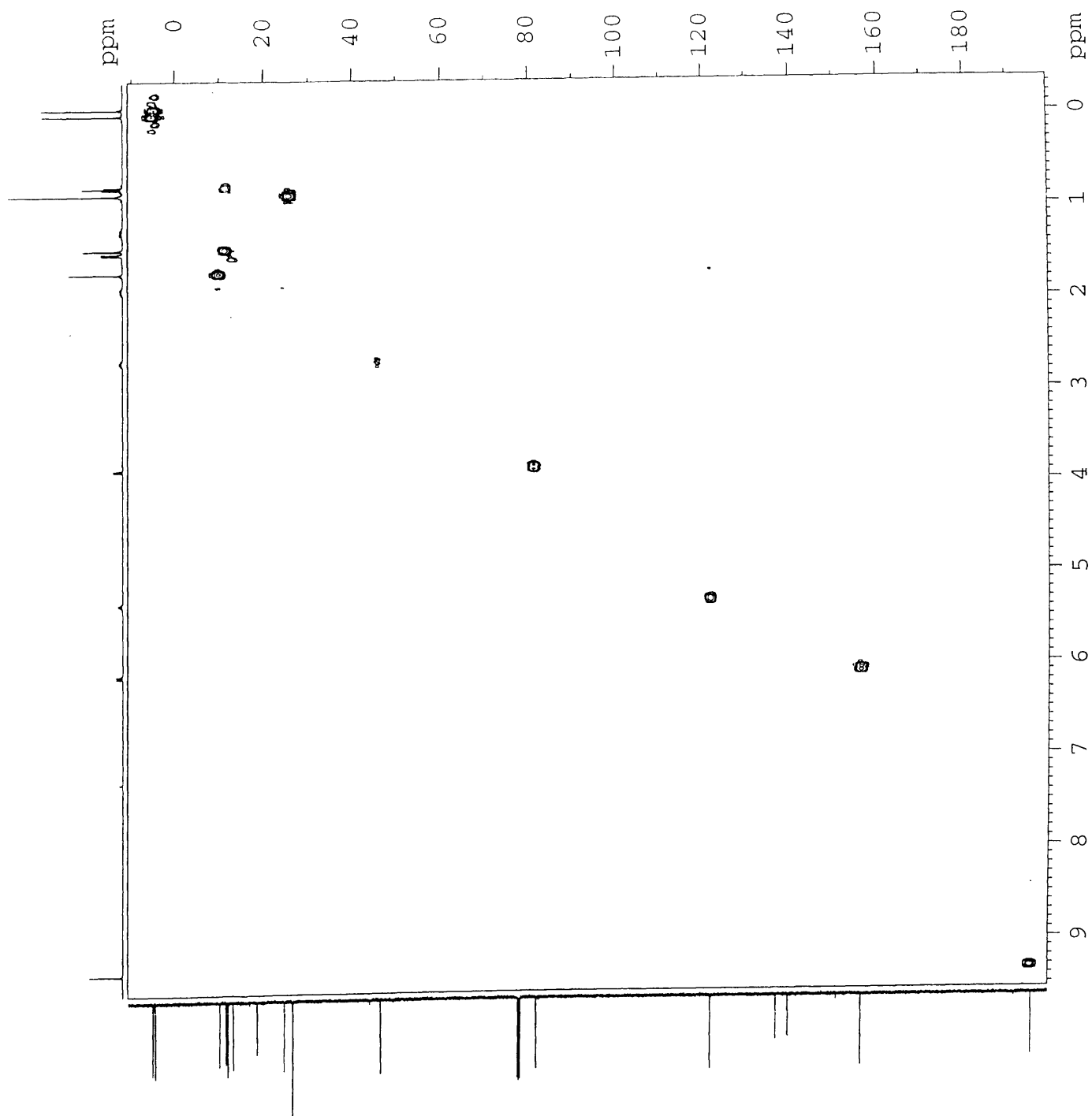


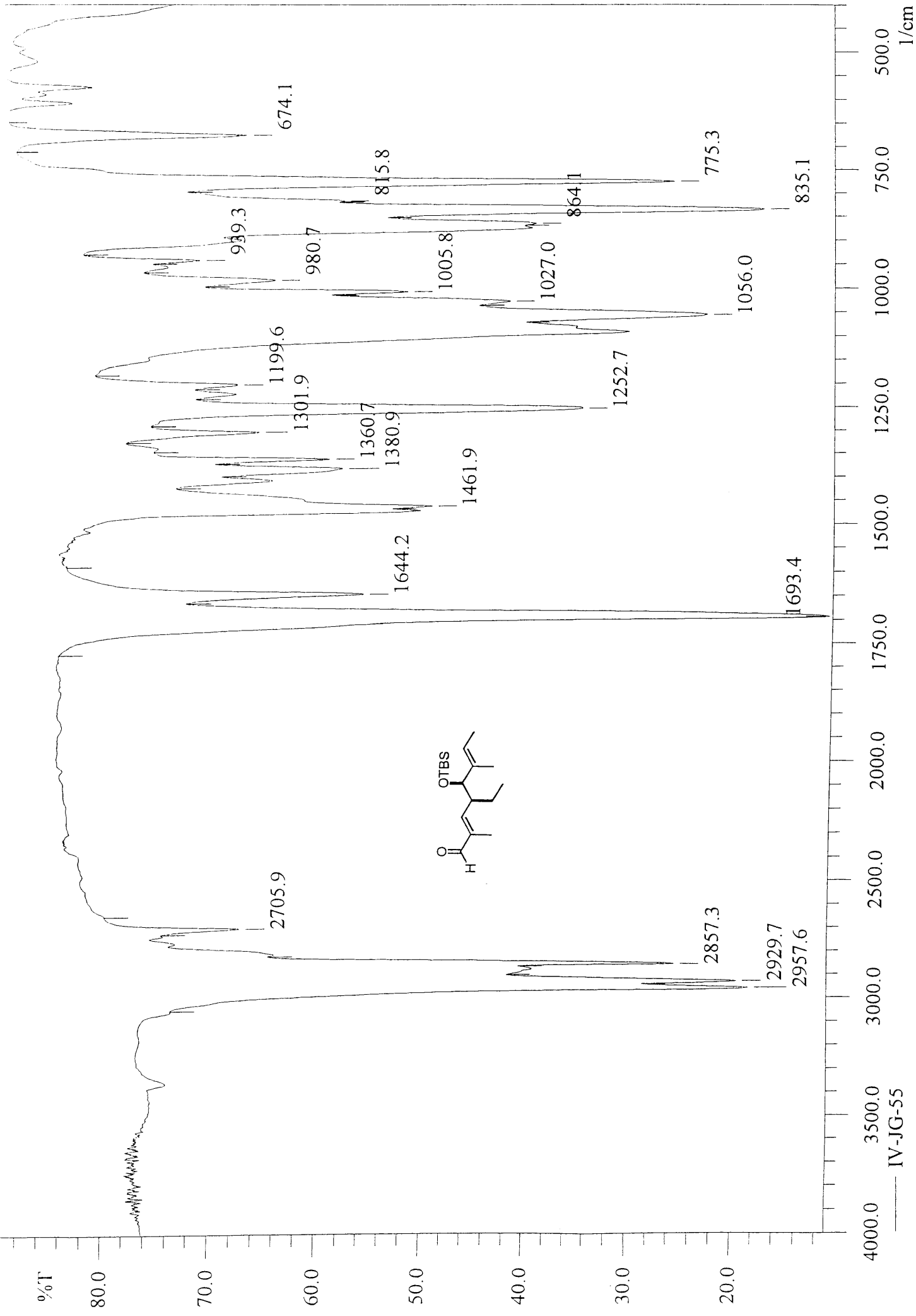
IV-JG-55  
DEPT  
CDCl<sub>3</sub>



IV-JG-55  
COSY  
CDC13



CC(C)=CC(=C)C(OTBS)C(C)=CC=O



01030406: Scan Avg 59-61 (10.77 - 11.13 min)

Base: 199.00 Int: 1.19568e+006 Sample: VG 70-SE Positive Ion FAB

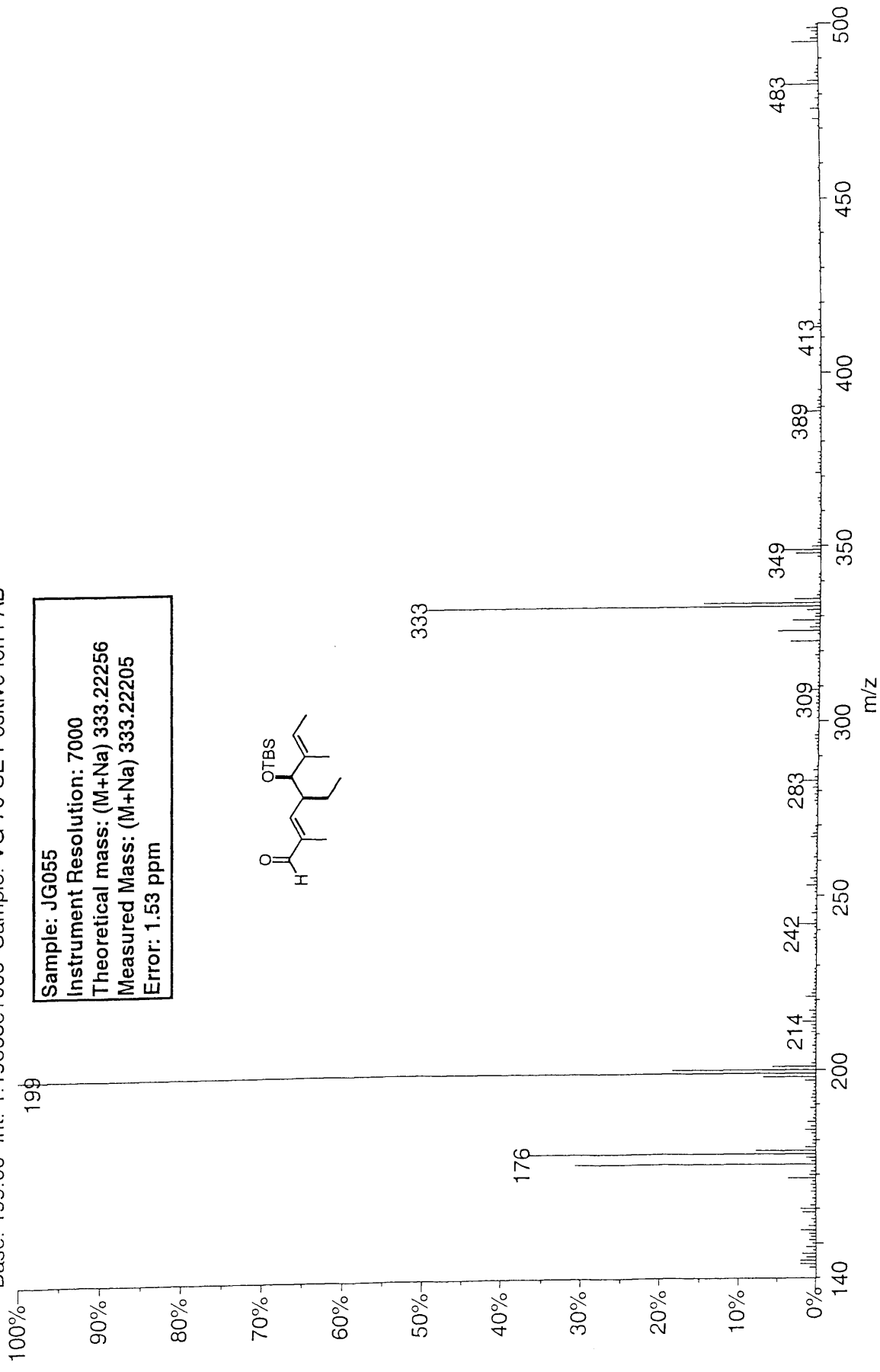
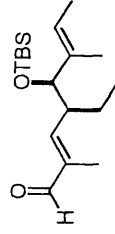
Sample: JG055

**Instrument Resolution: 7000**

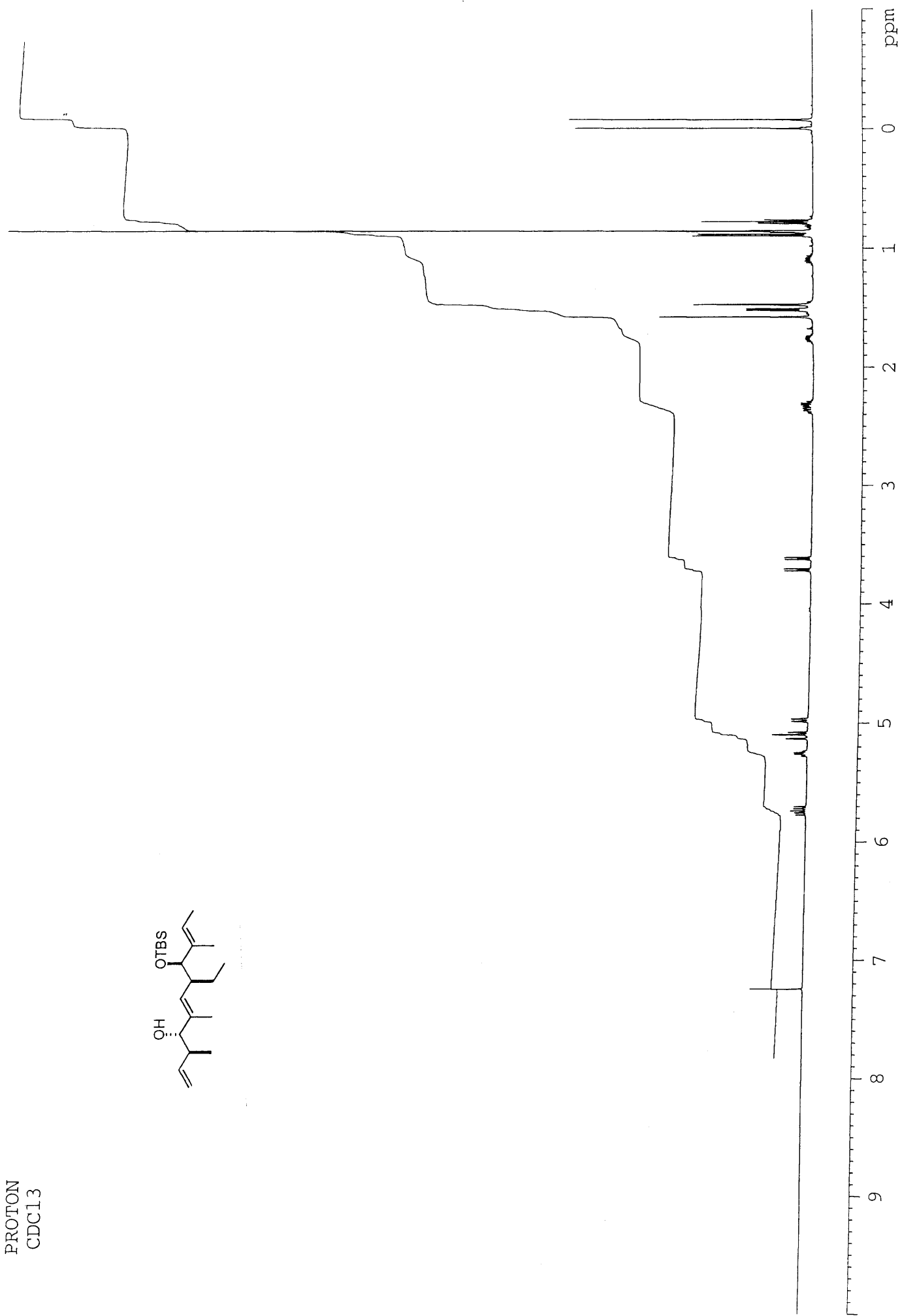
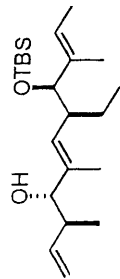
Theoretical mass: (M+Na) 333.22256

Measured Mass: (M+Na) 333.22205

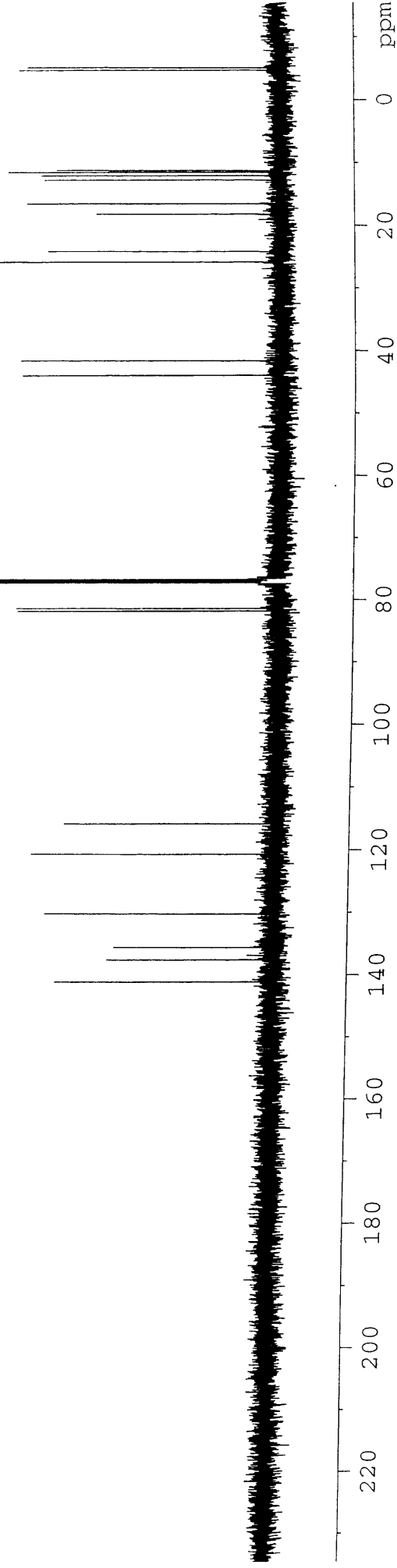
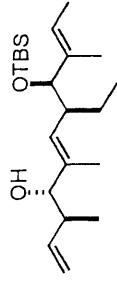
Error: 1.53 ppm



IV-JG-59a  
PROTON  
CDCl<sub>3</sub>



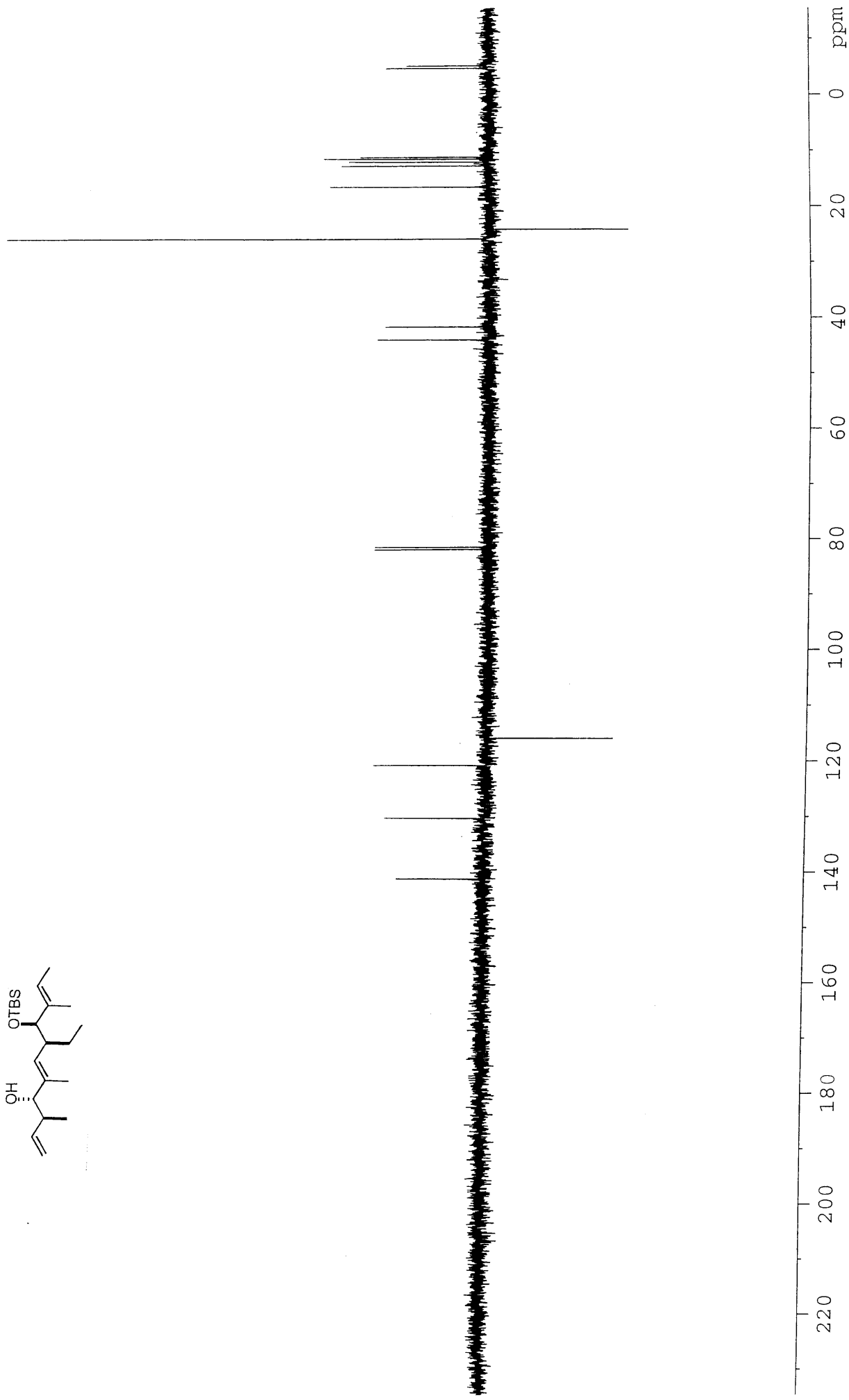
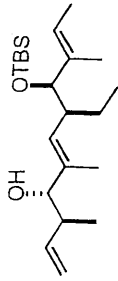
IV-JG-59a  
CARBON  
CDCl<sub>3</sub>



IV-JG-59a

DEPT

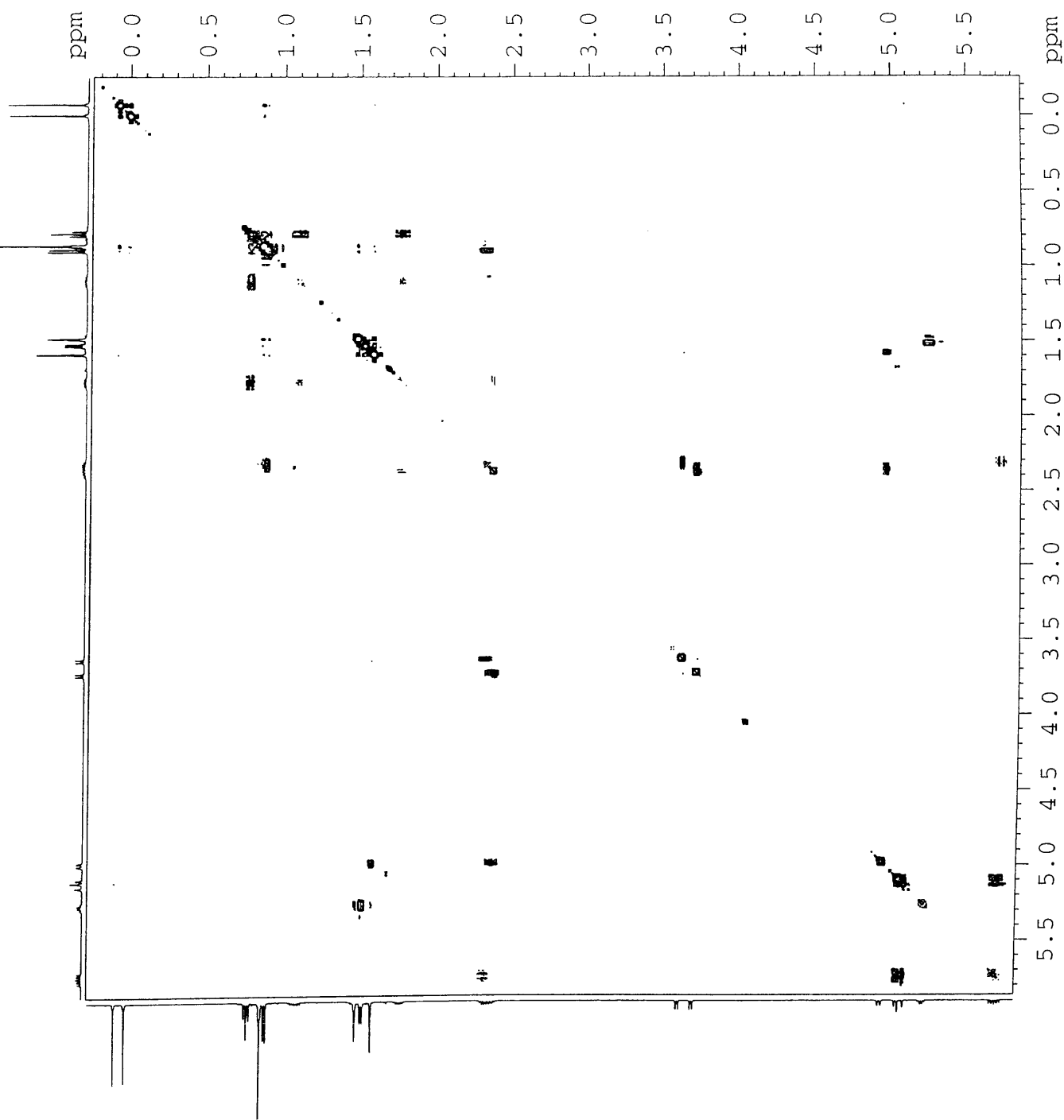
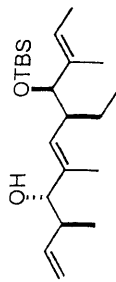
CDC13

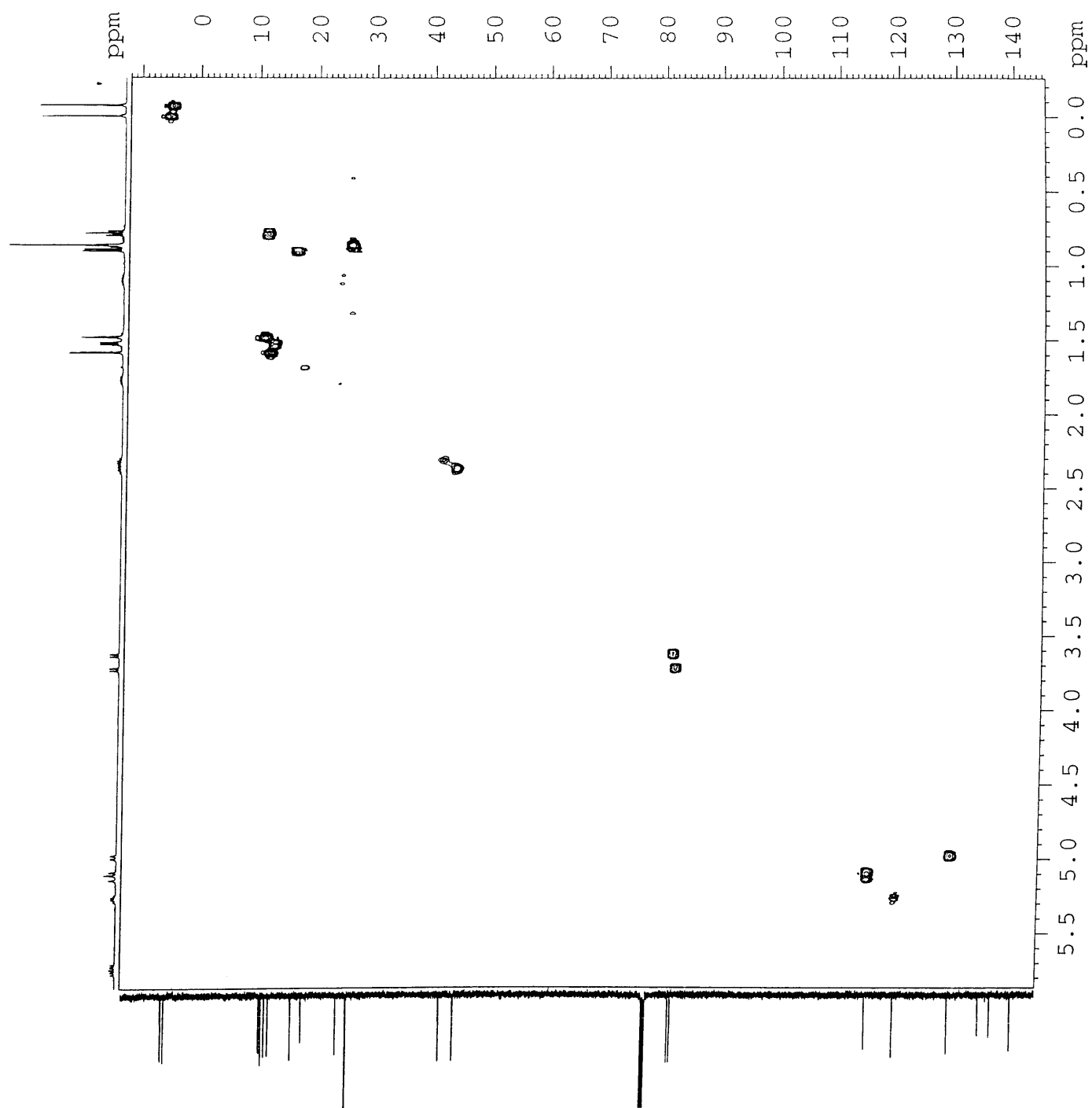


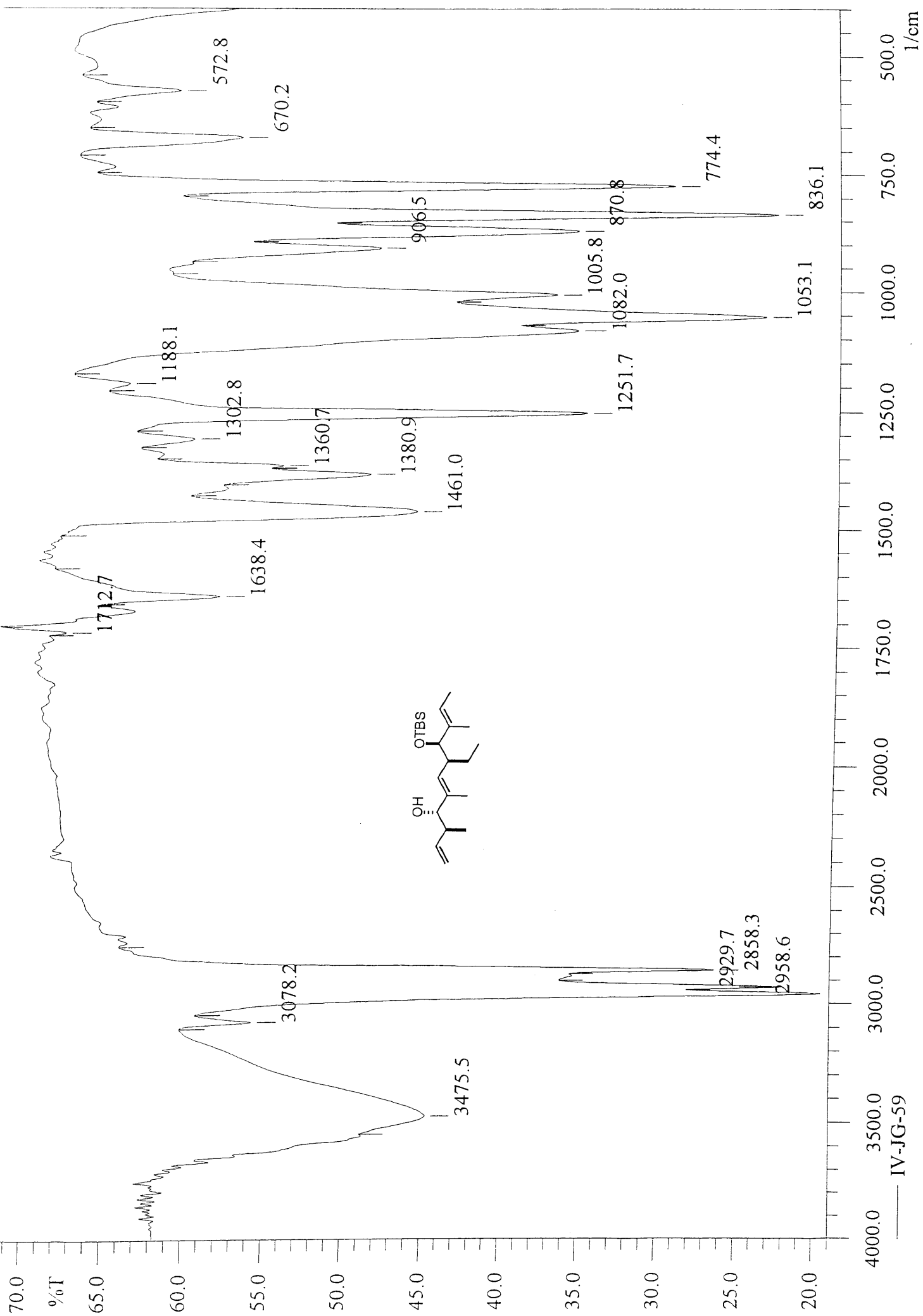


COSY

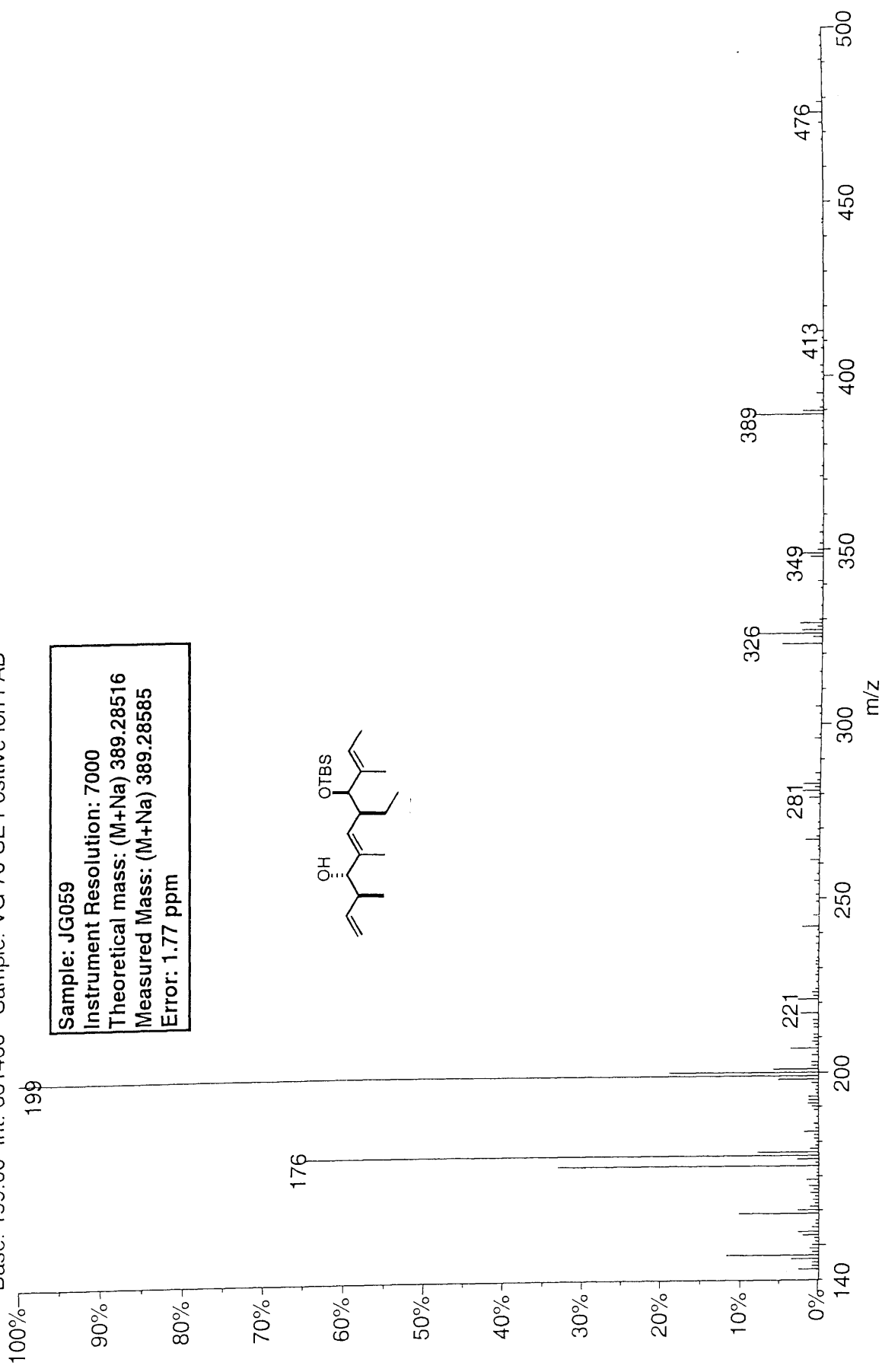
CDC13



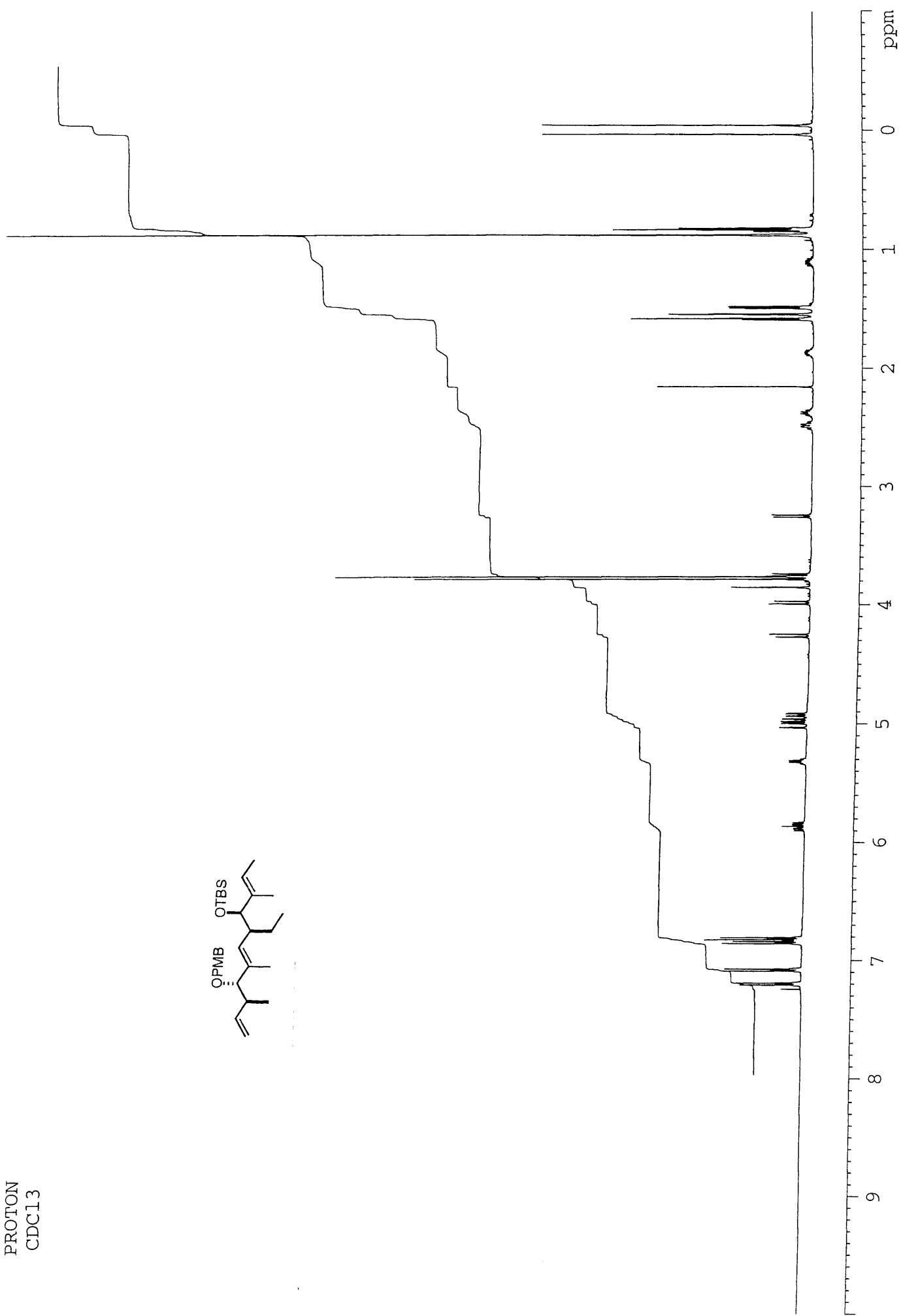
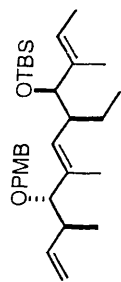
CC(C)=CC(O)C=C(C)C(OTBS)C=C(C)C



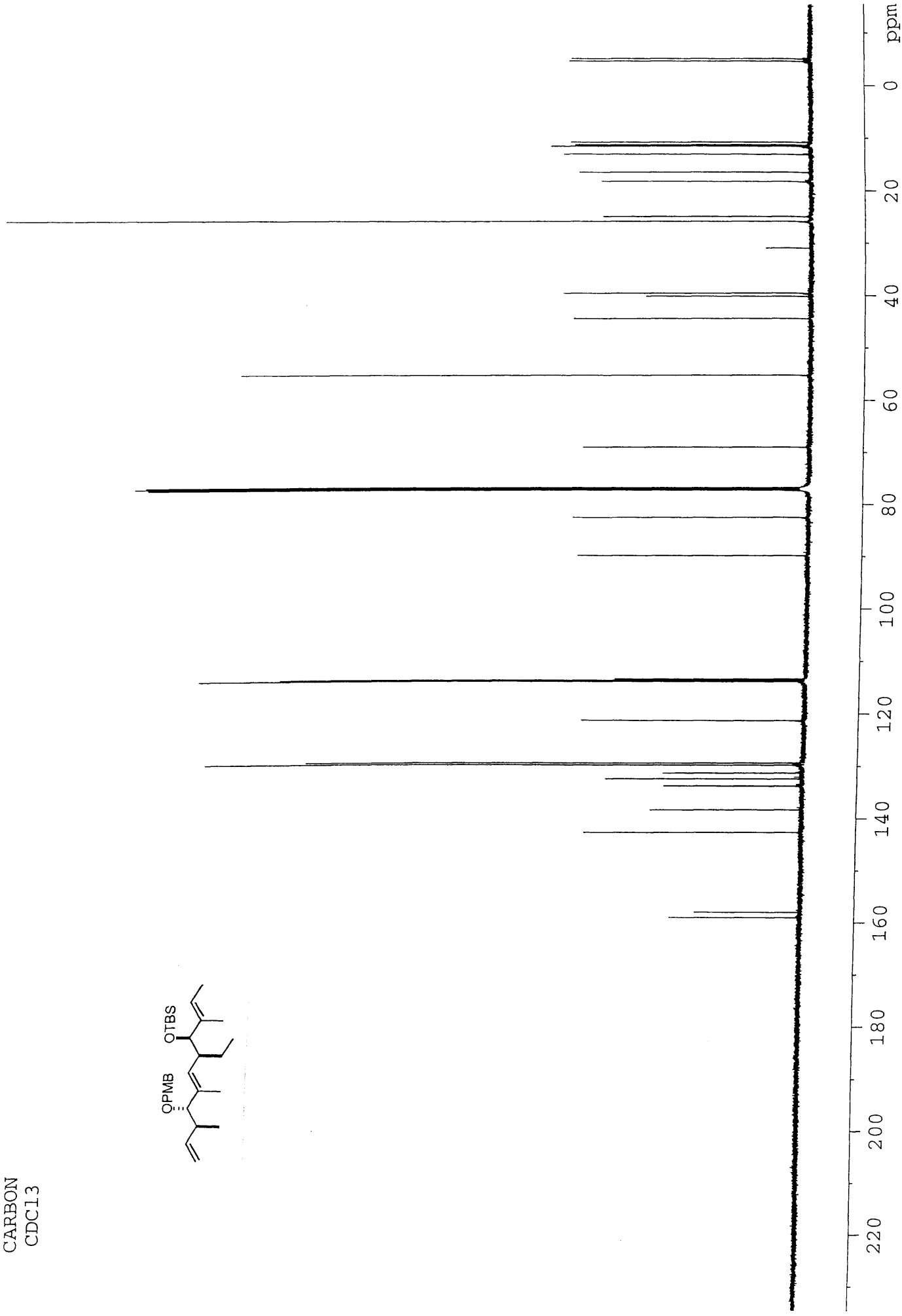
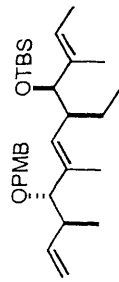
01030406: Scan 42 (7.65 min)  
Base: 199.00 Int: 661460 Sample: VG 70-SE Positive Ion FAB



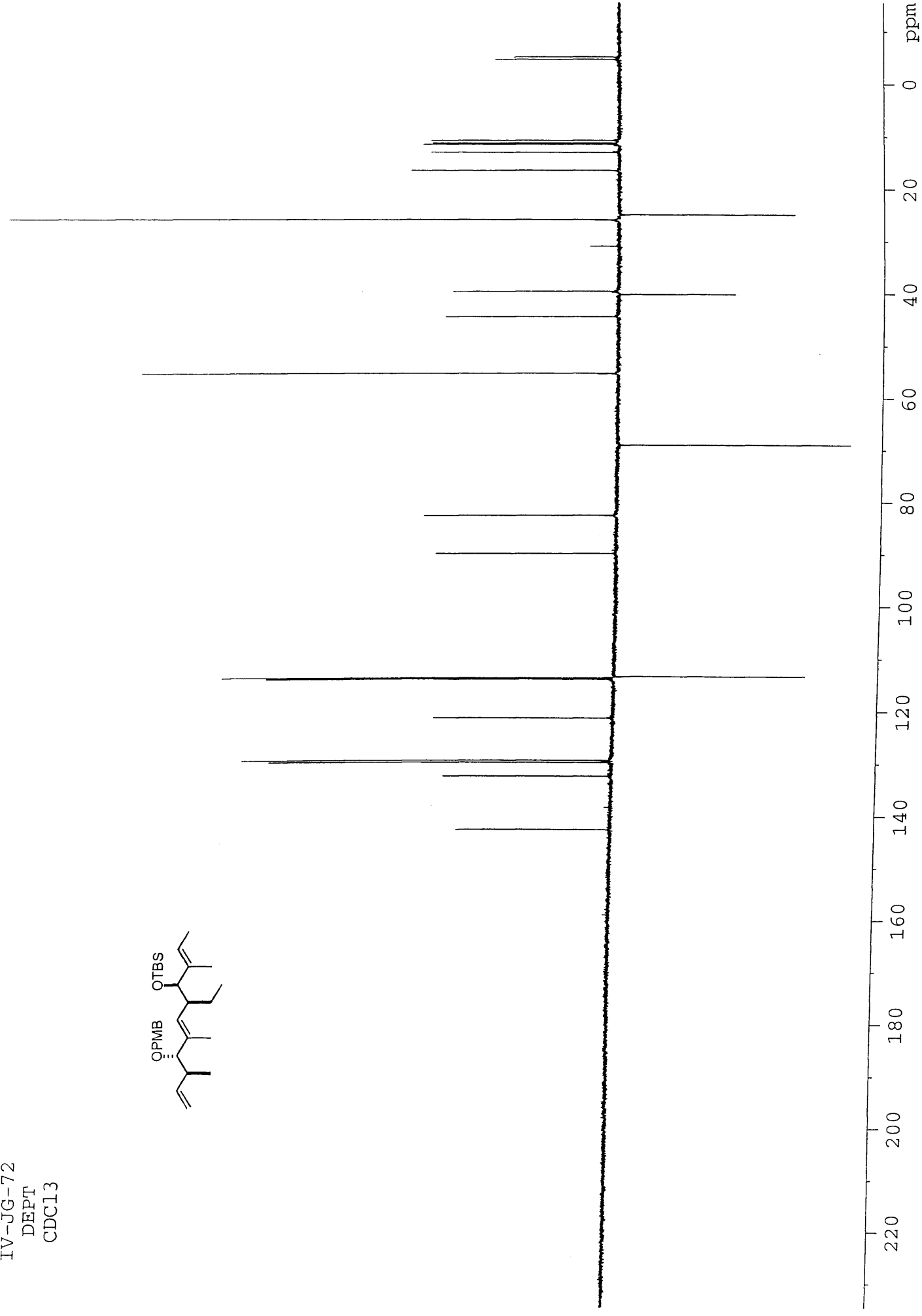
IV-JG-72  
PROTON  
CDCl3



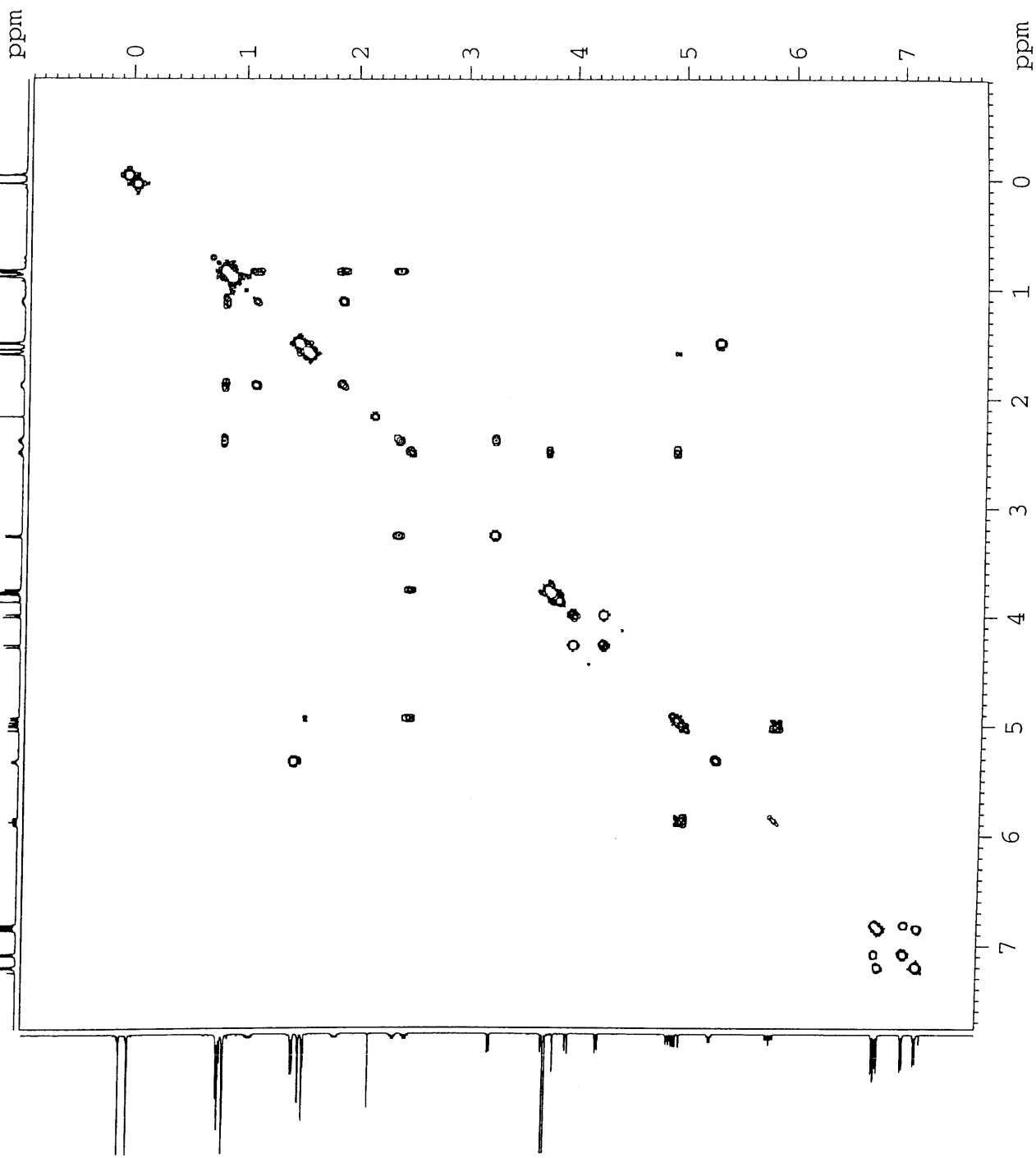
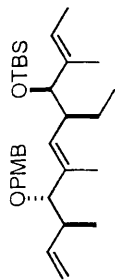
IV-JG-72  
CARBON  
CDCl<sub>3</sub>



Chemical structure of compound 10: A branched alkene with a vinyl group, a PMB group, and an OTBS group.

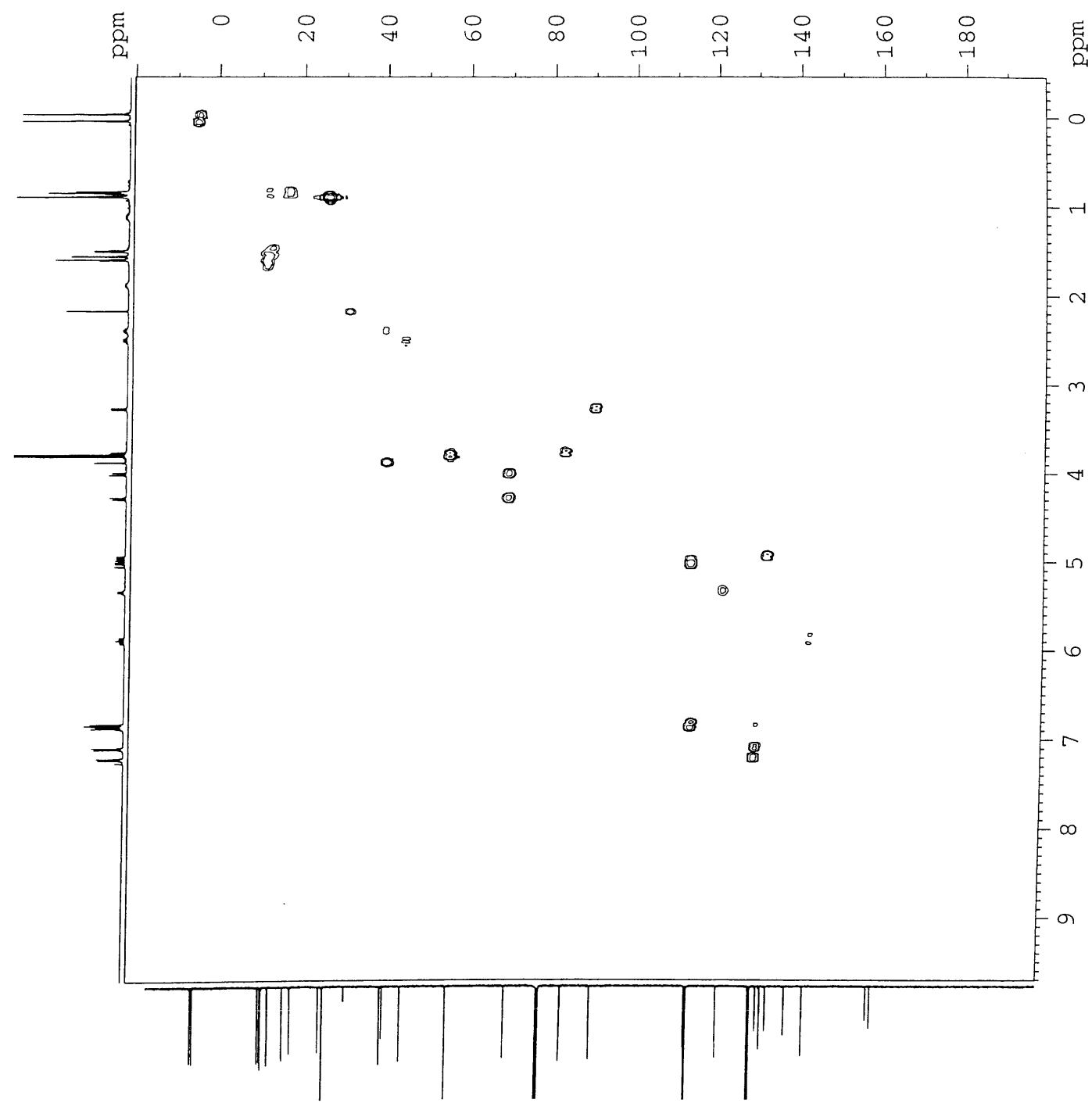


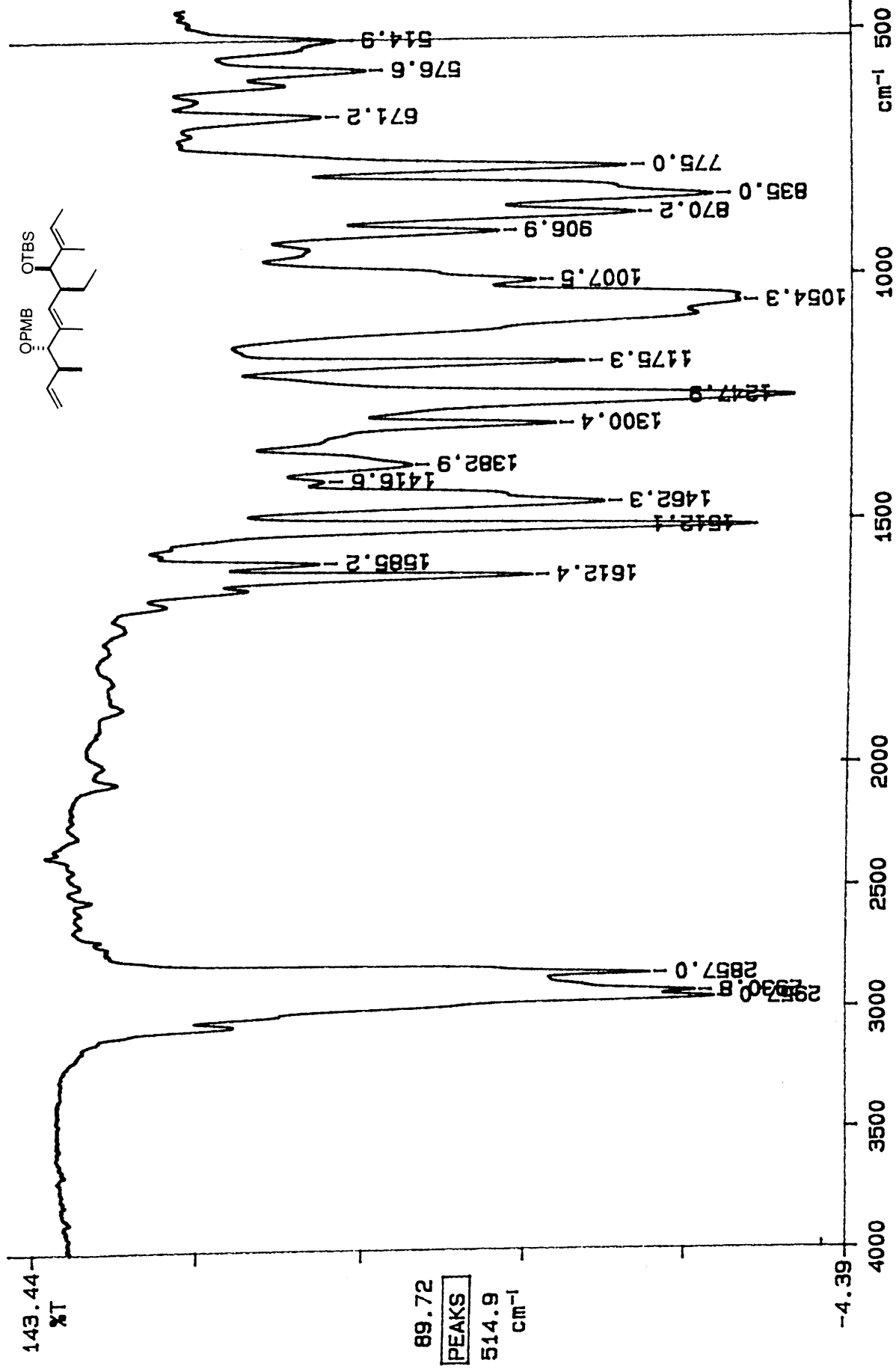
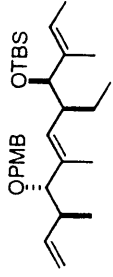
IV-JG-72  
COSY  
CDC13



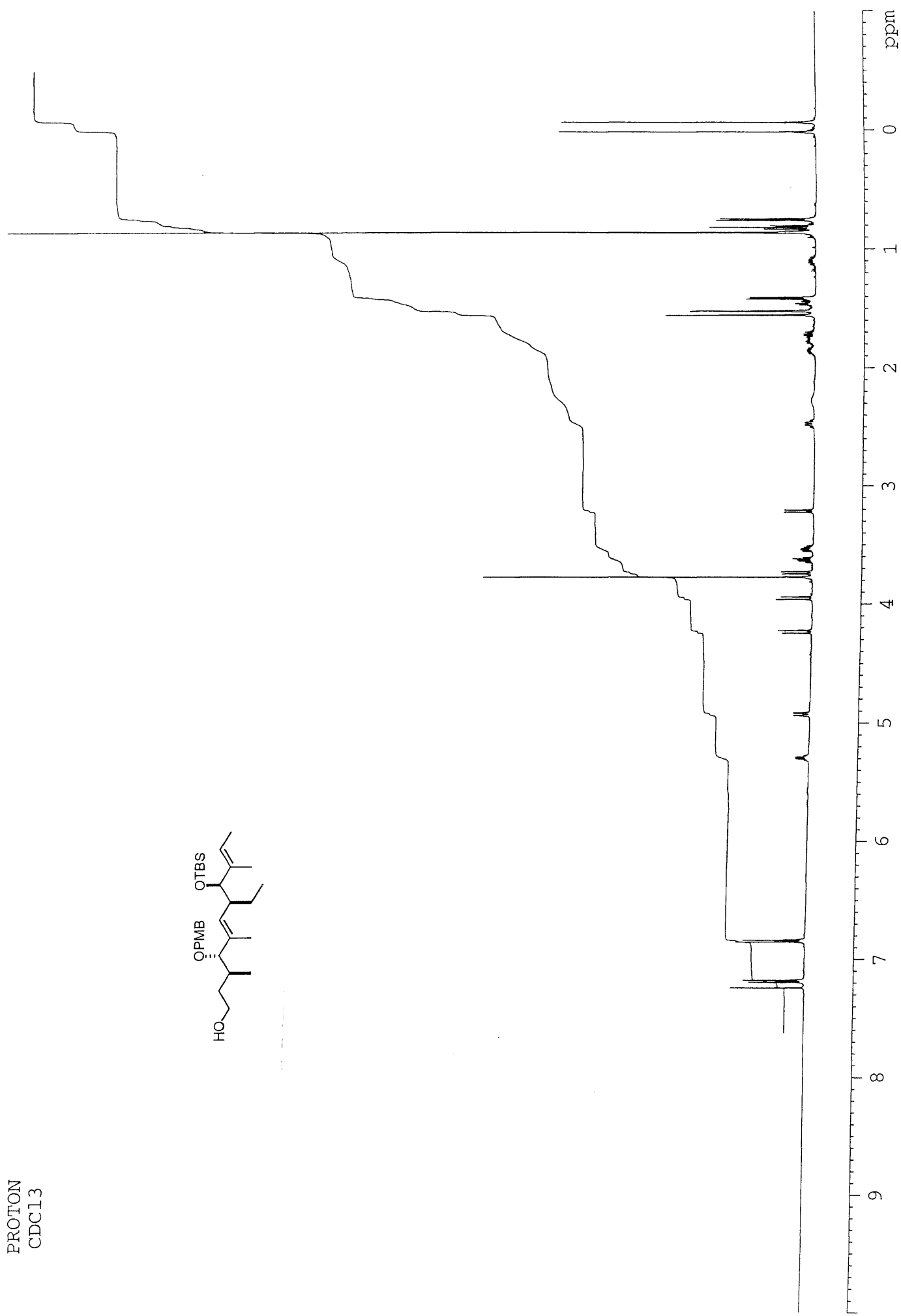
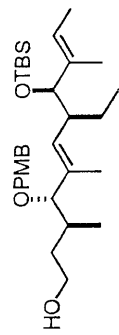


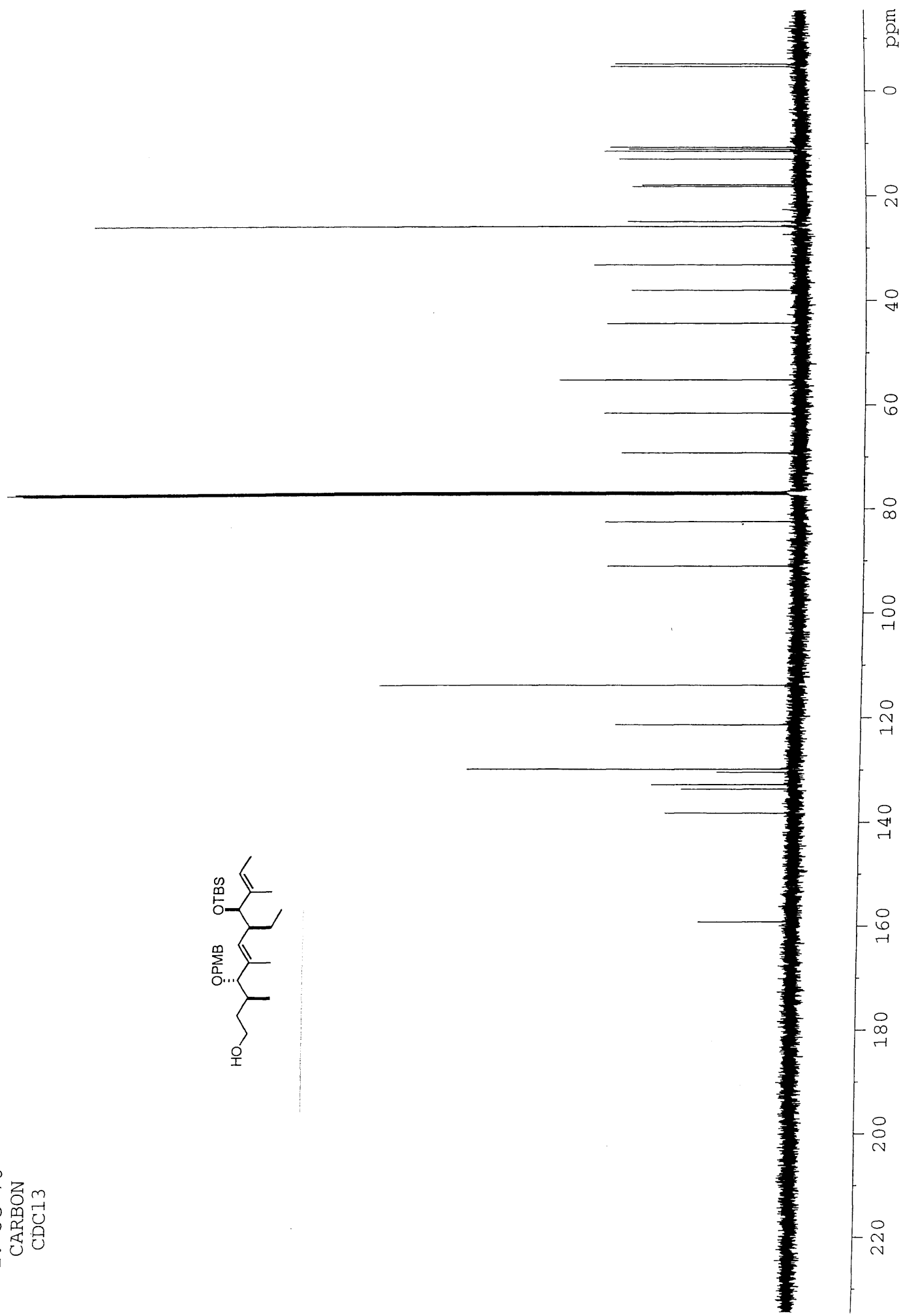
Chemical structure of compound 10: A branched alkene with a PMB group on a dashed bond and an OTBS group on a solid bond.



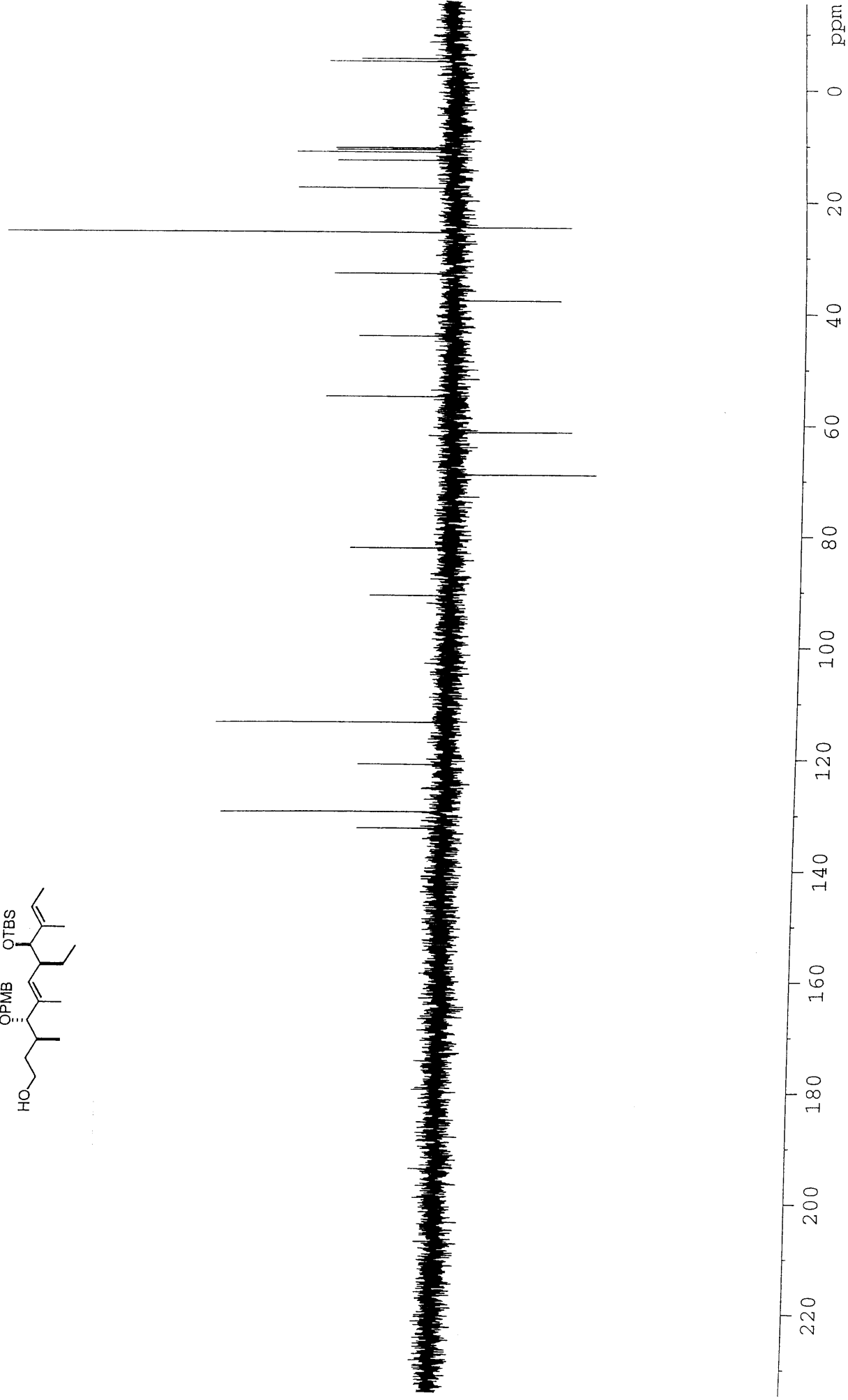
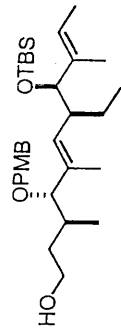


IV-JG-76  
PROTON  
CDCl<sub>3</sub>

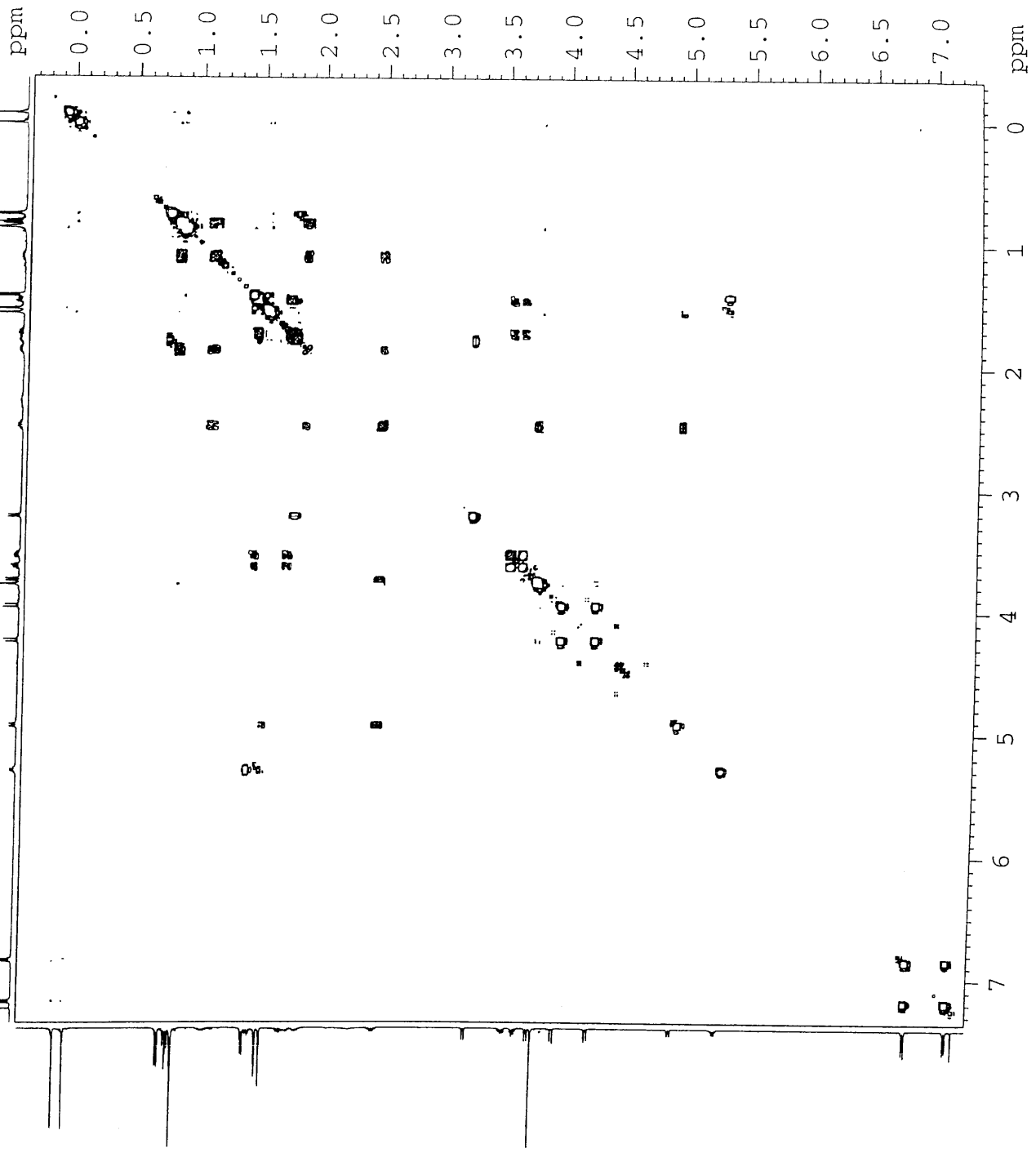
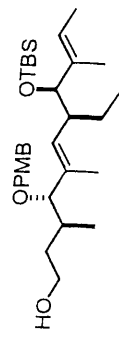


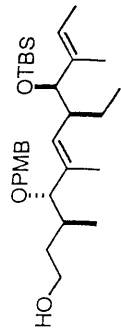
C[C@H](O)C[C@@H](OC(=O)c1ccc(C=C)cc1)[C@H](C)/C=C/[C@H](C)C(=C)C[Si](C)(C)C

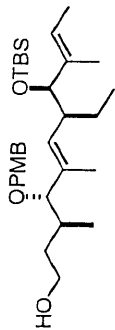
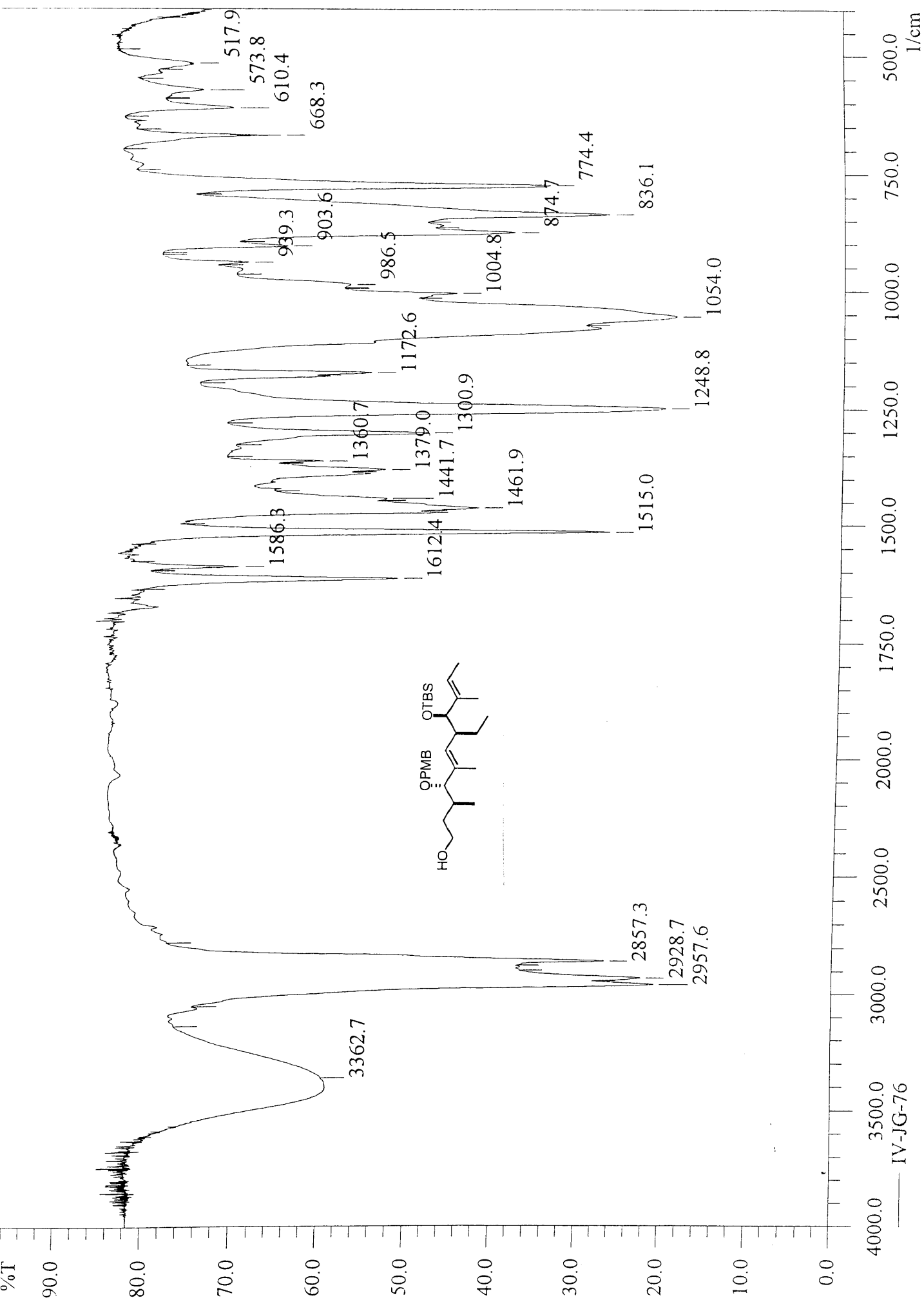
IV-JG-76  
DEPT  
CDC13



CDC13

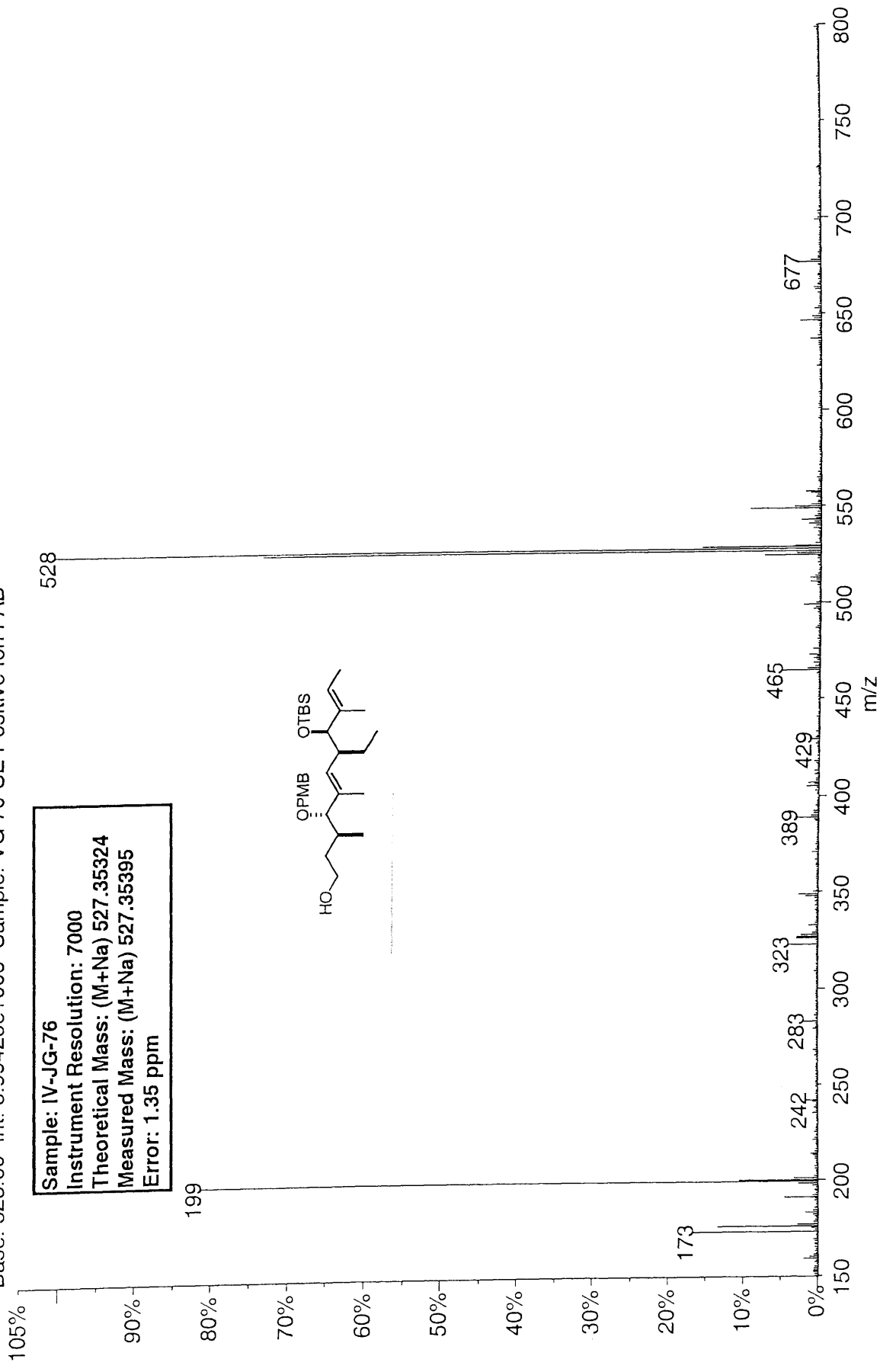




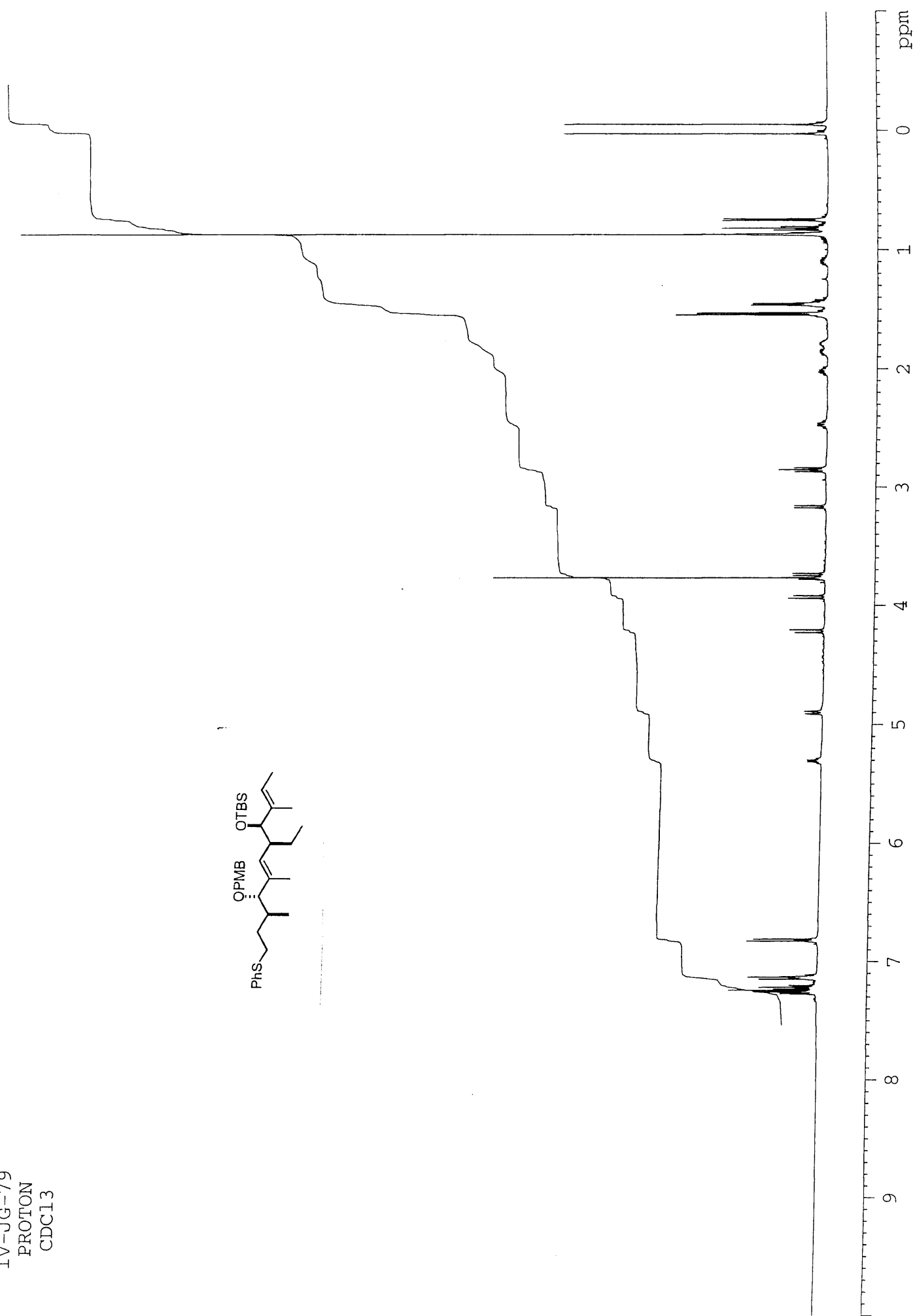
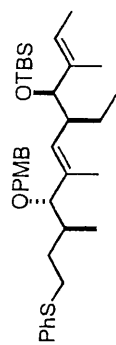


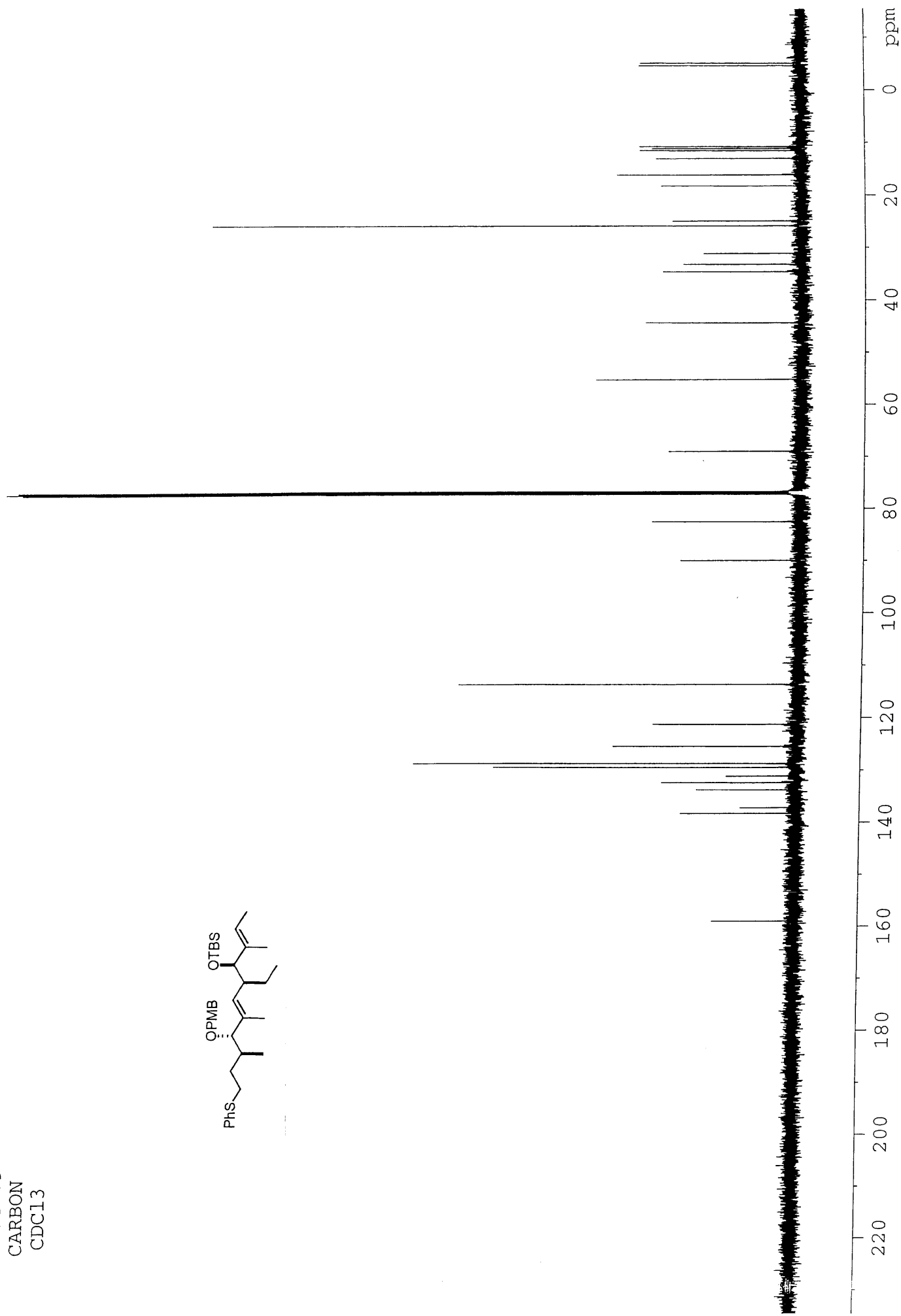


01020206: Scan Avg 9-10 (1.60 - 1.78 min) - Back  
Base: 528.00 Int: 3.99423e+006 Sample: VG 70-SE Positive Ion FAB



IV-JG-79  
PROTON  
CDC13

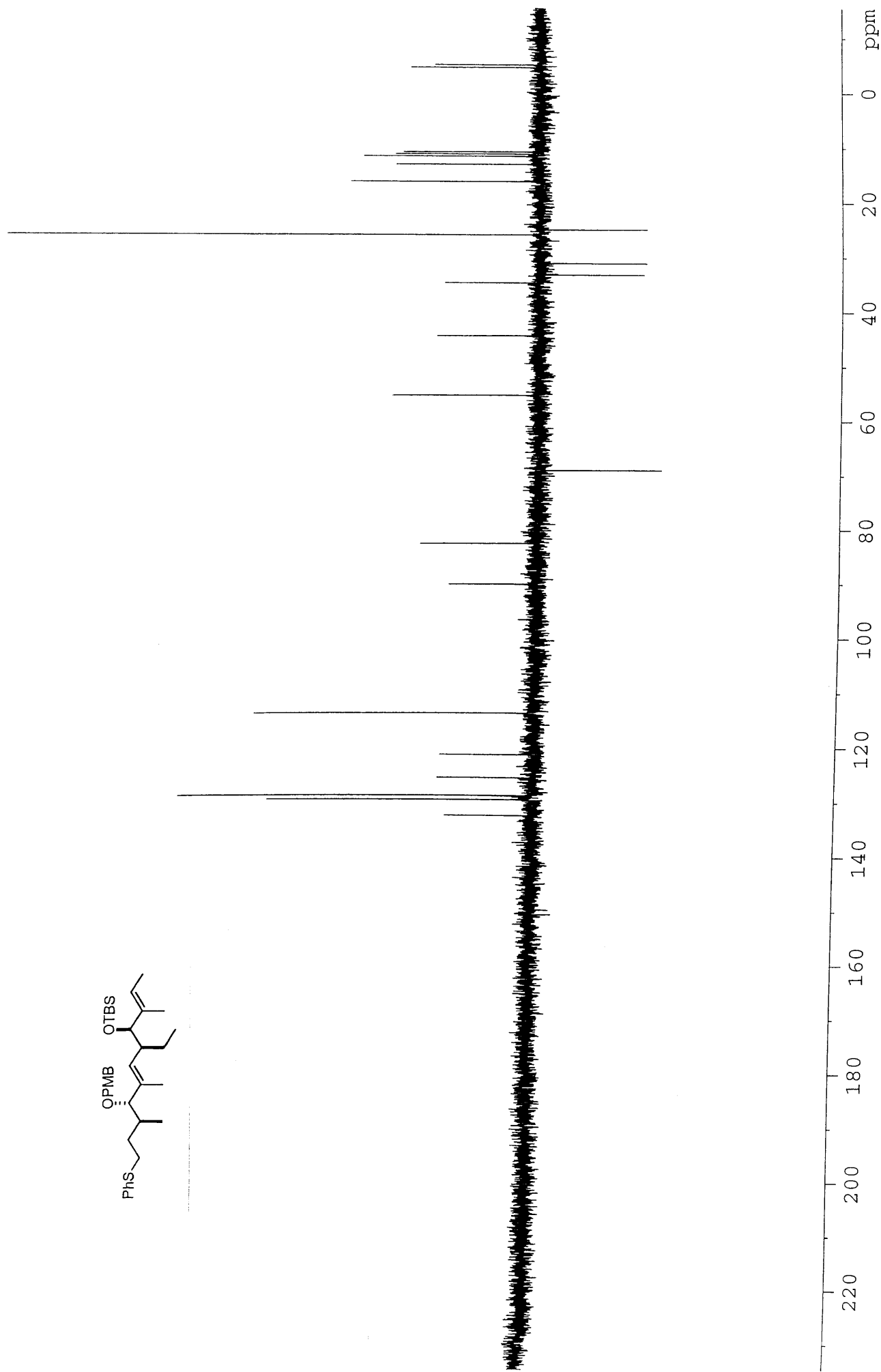
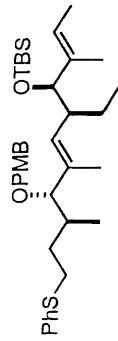


C[C@H](C)[C@@H](OPMB)C(=C)[C@H](OBSi(C)(C)C)C=C

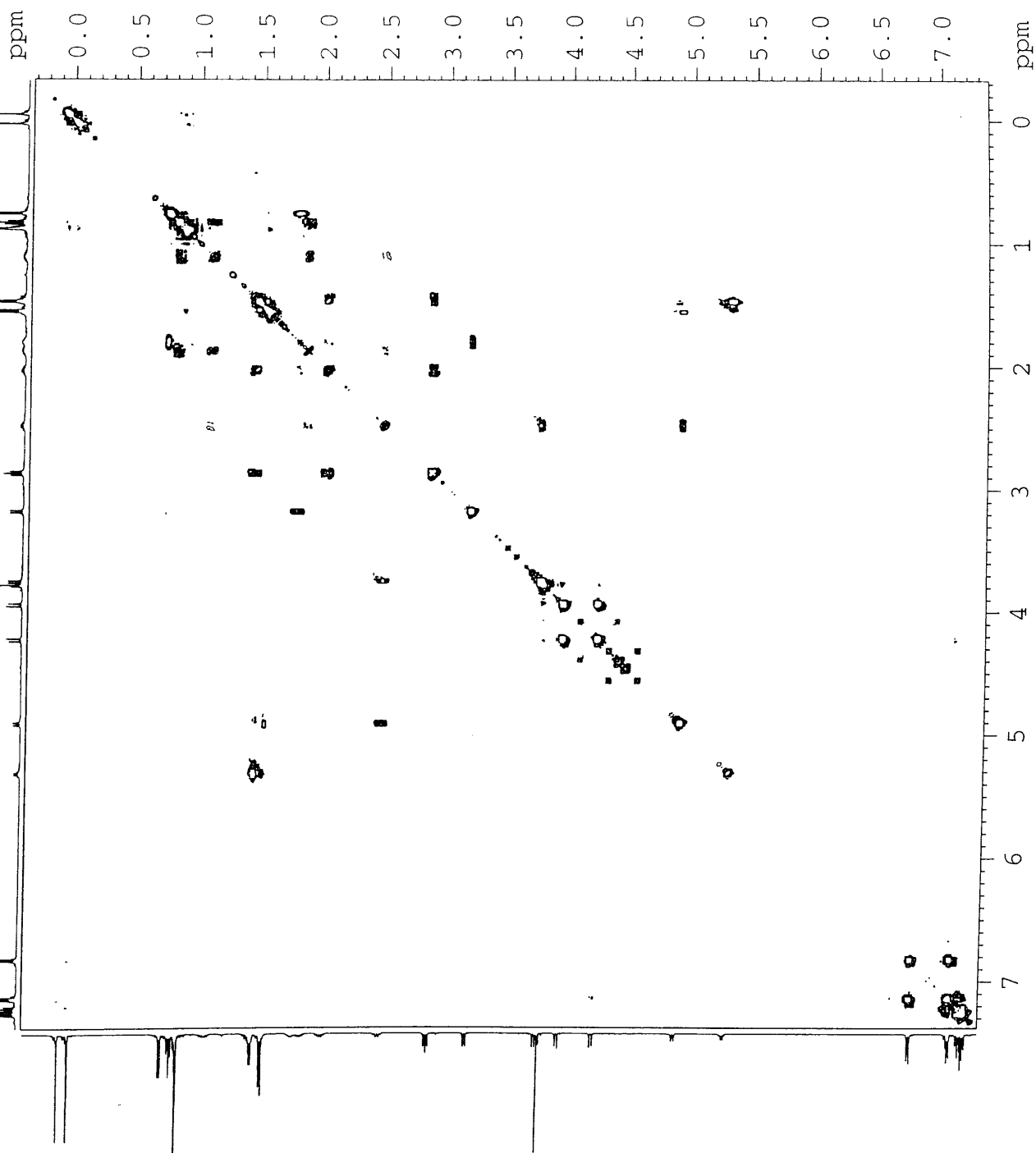
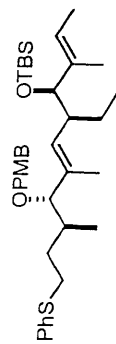
IV-JG-79

DEPT

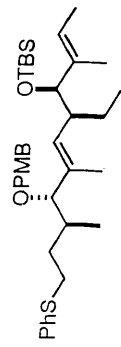
CDCl<sub>3</sub>

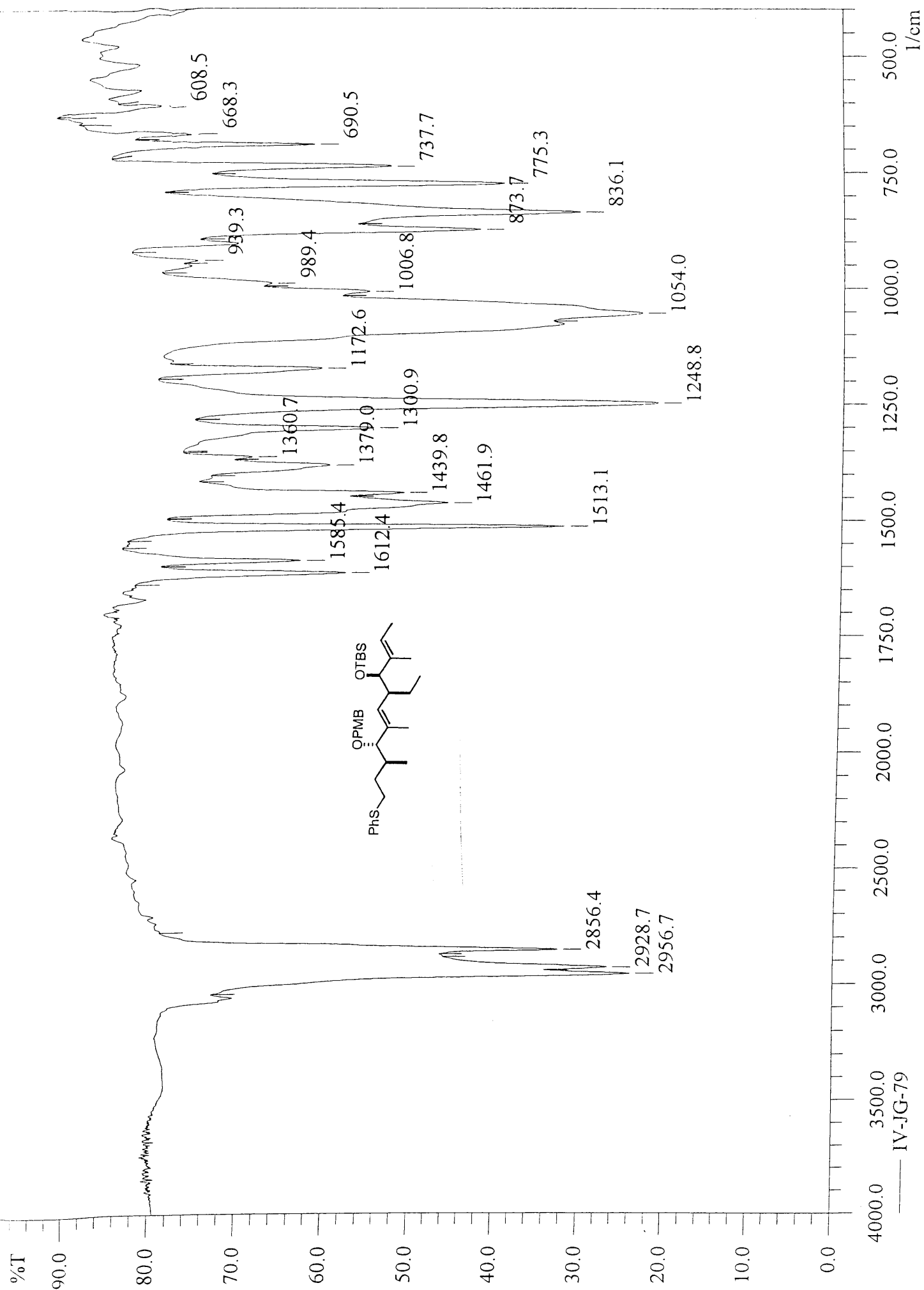


CDCL3



2D NMR spectrum of compound 10. The x-axis represents  $^1\text{H}$  chemical shift (ppm) from 0 to 7.5, and the y-axis represents  $^{13}\text{C}$  chemical shift (ppm) from 0 to 160. The spectrum shows correlations between protons and carbons, with a 1D  $^1\text{H}$  NMR spectrum along the top and a 1D  $^{13}\text{C}$  NMR spectrum along the left. Key peaks are labeled with numbers 1 through 17.





01020206: Scan Avg 30-32 (5.45 - 5.82 min) - Back  
Base: 199.00 Int: 2.67135e+006 Sample: VG 70-SE Positive Ion FAB

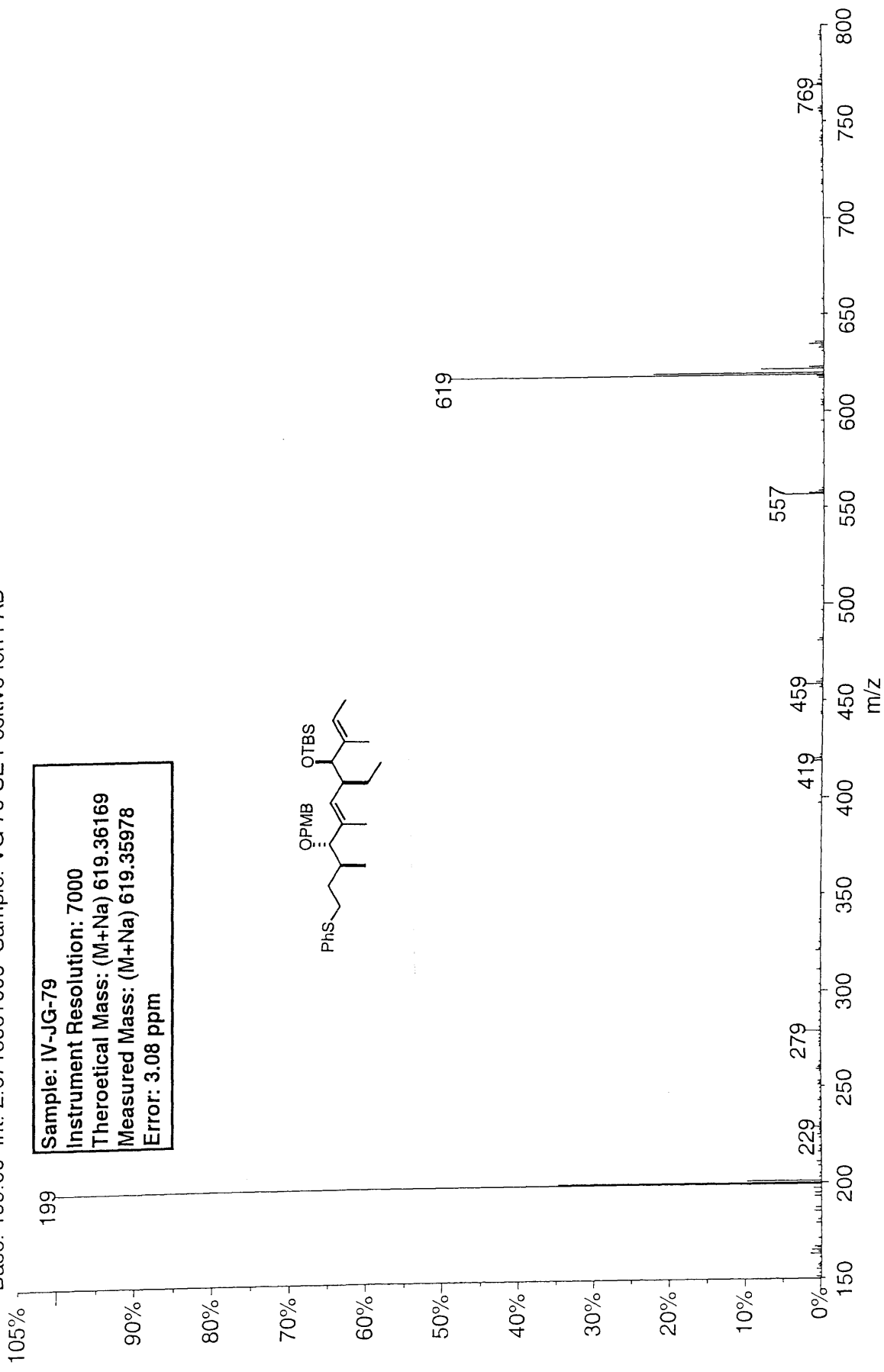
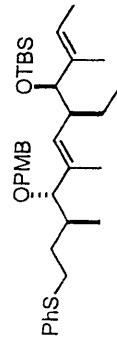
Sample: IV-JG-79

**Instrument Resolution: 7000**

**Theoretical Mass: (M+Na) 619.36169**

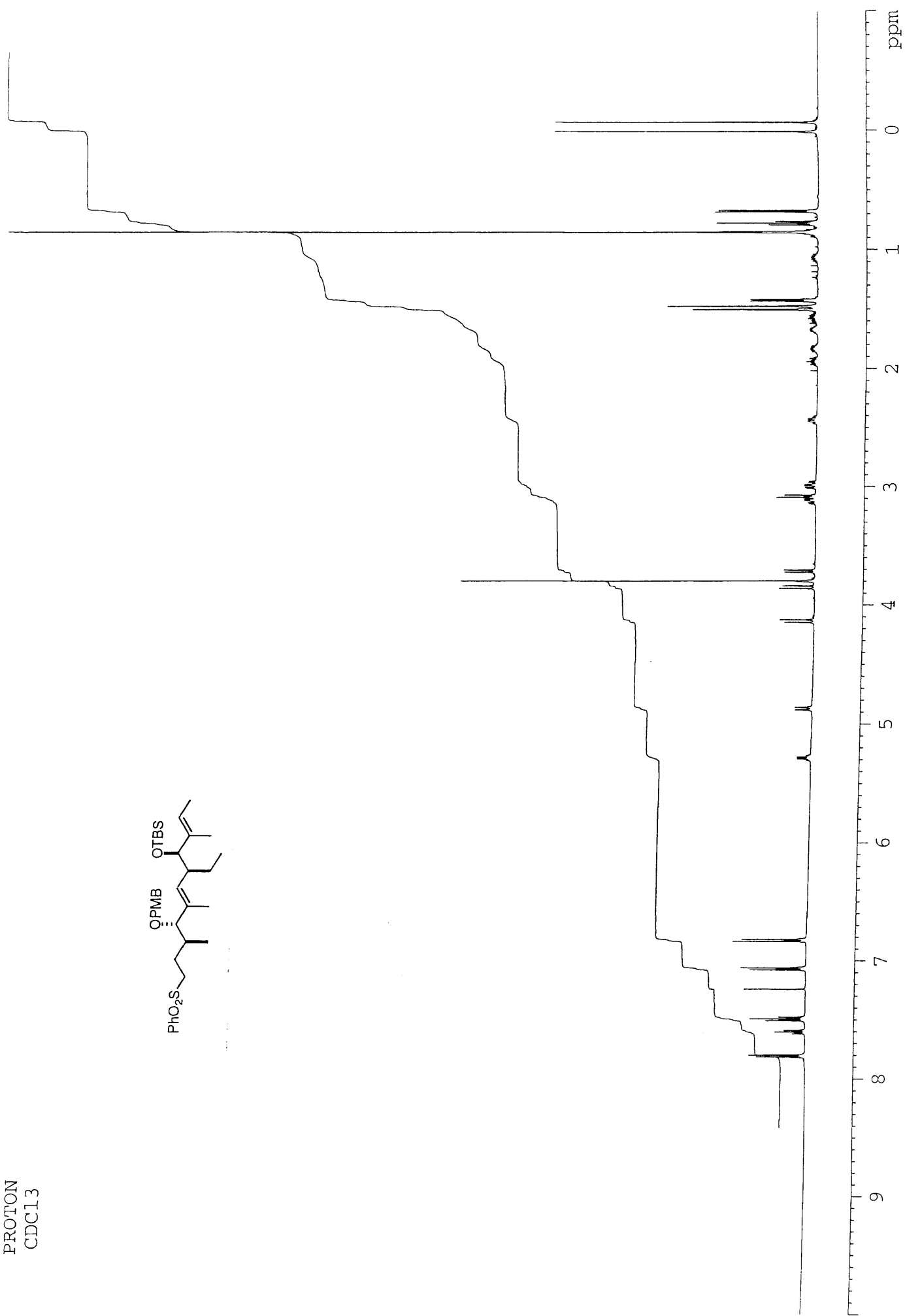
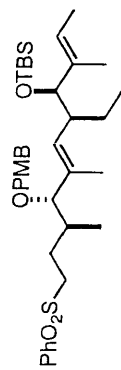
Measured Mass: (M+Na) 619.35978

**Error: 3.08 ppm**

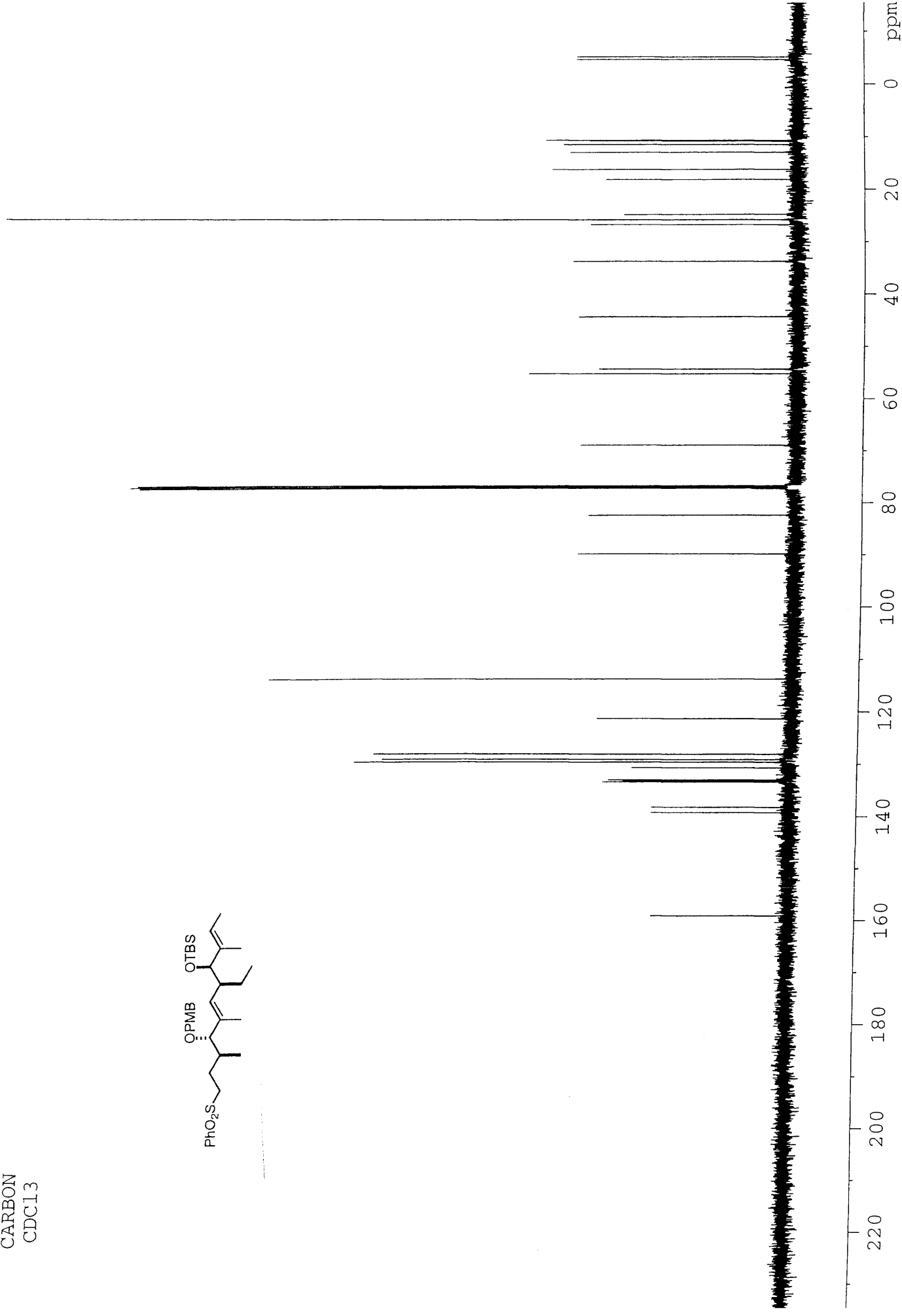
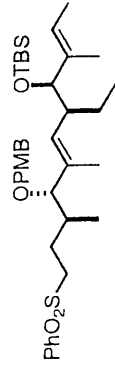




IV-JG-82  
PROTON  
CDC13



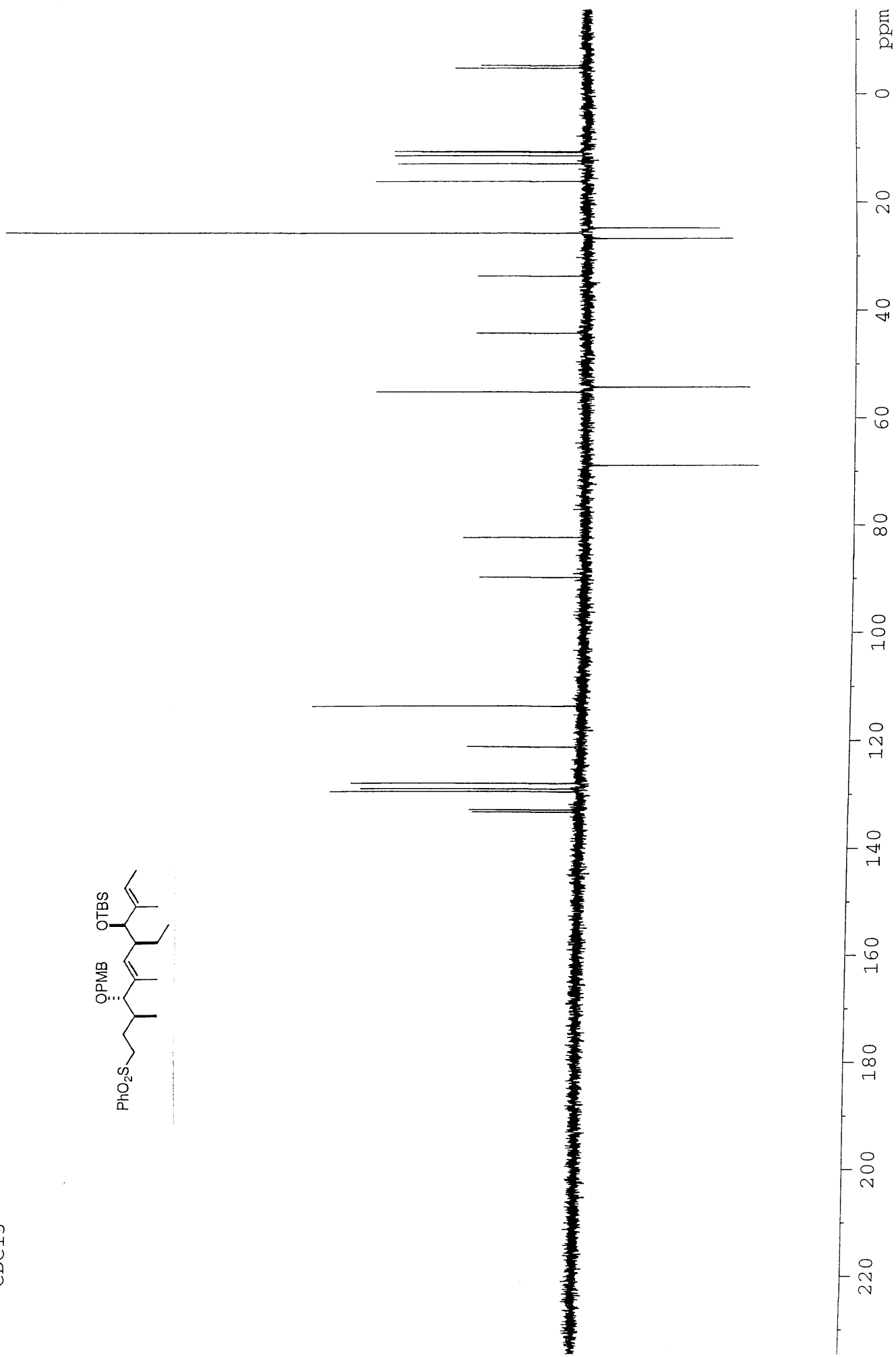
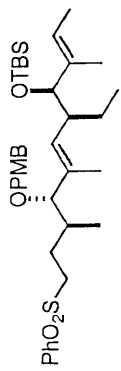
IV-JG-82  
CARBON  
CDCl<sub>3</sub>



IV-JG-82

DEPT

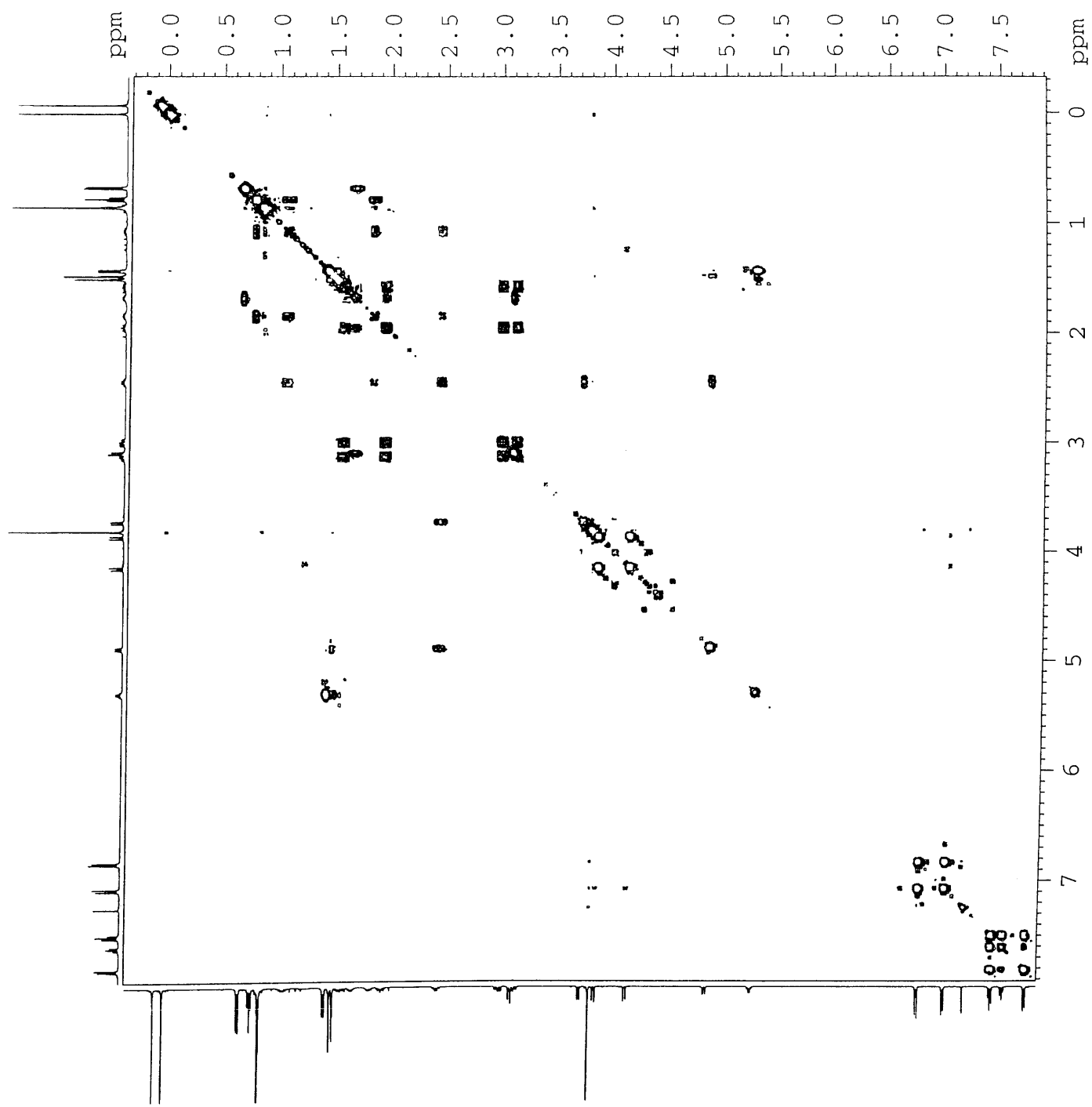
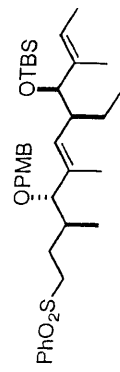
CDC13



IV-JG-82

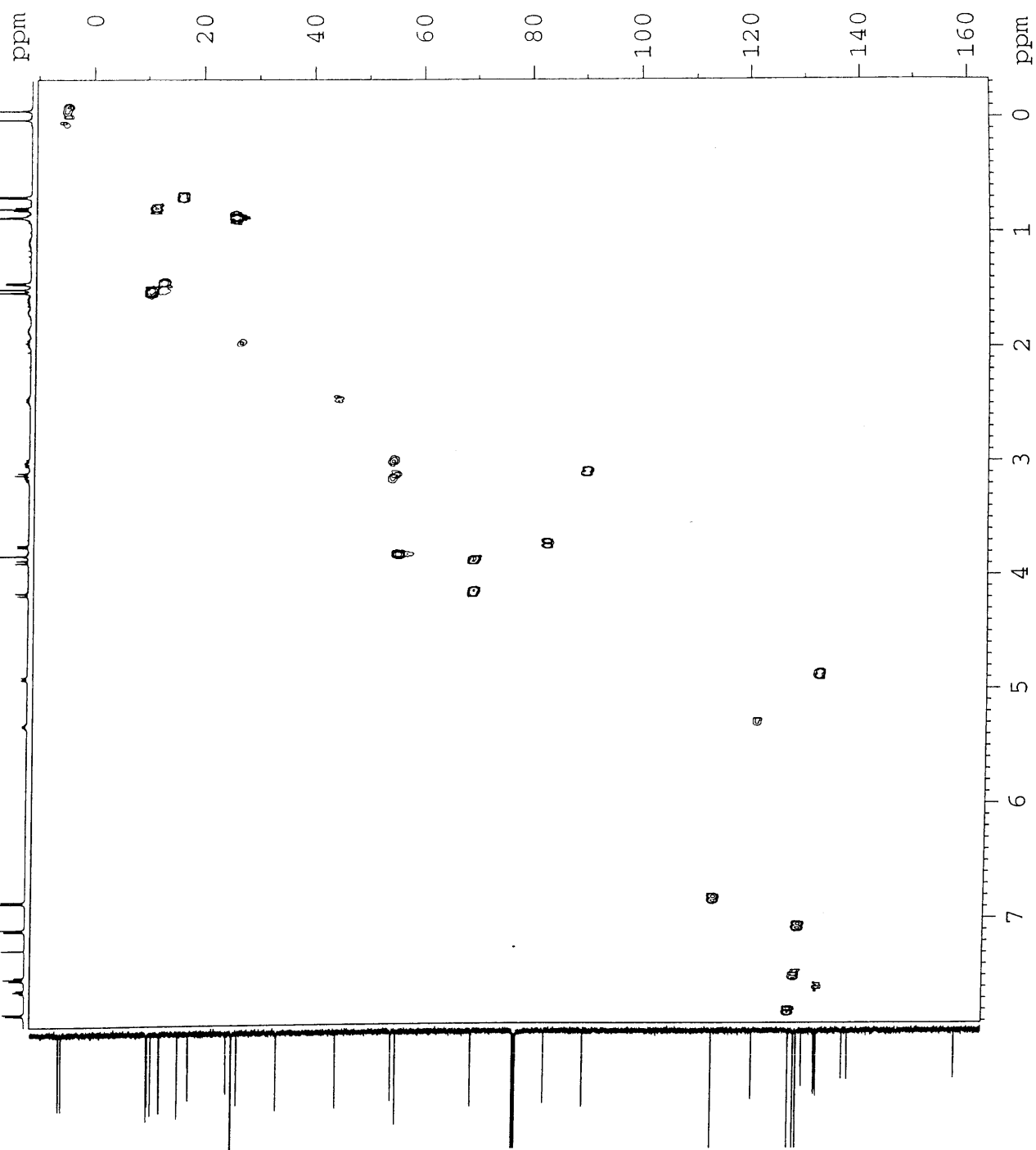
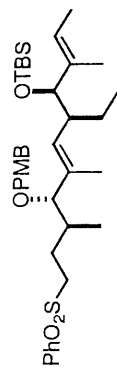
COSY

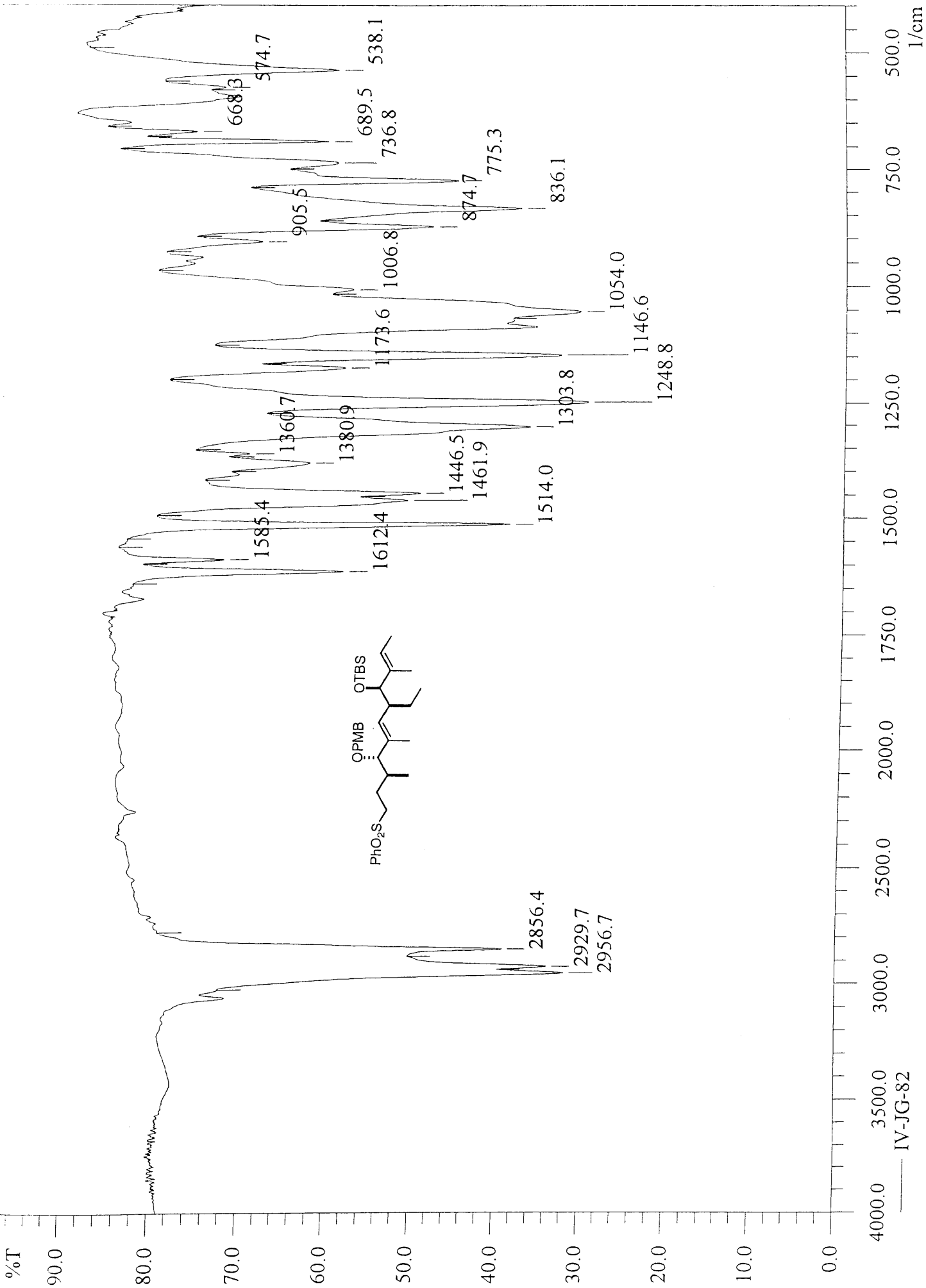
CDC13



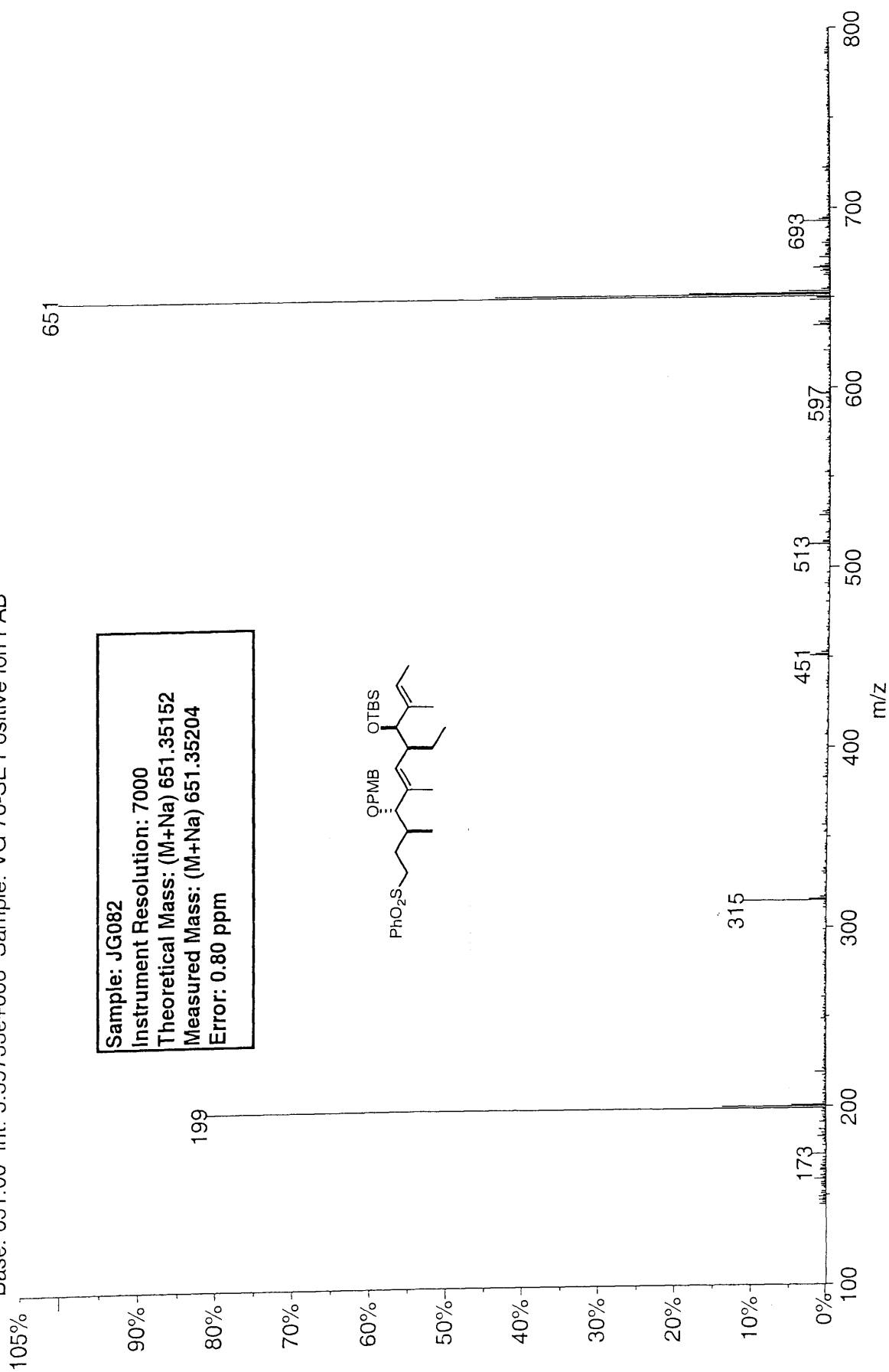
HMQC

CDC13





01270206: Scan 275 (50.37 min) - Back  
Base: 651.00 Int: 5.59733e+006 Sample: VG 70-SE Positive Ion FAB



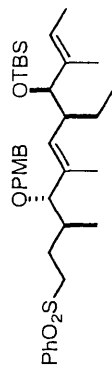
Sample: JG082

Instrument Resolution: 7000

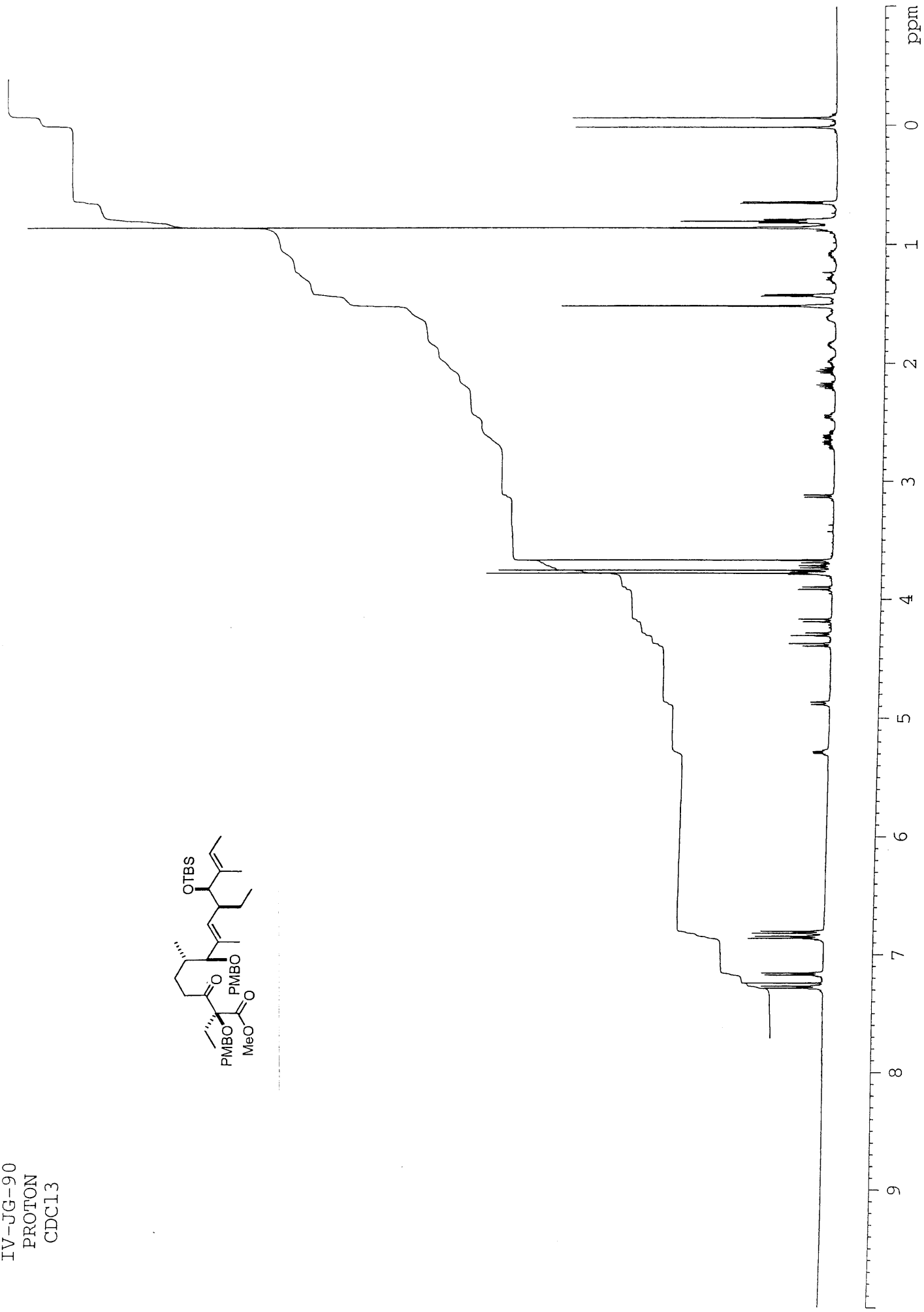
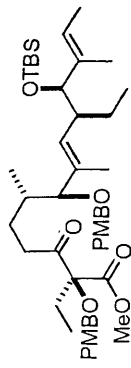
Theoretical Mass: (M+Na) 651.35152

Measured Mass: (M+Na) 651.35204

Error: 0.80 ppm

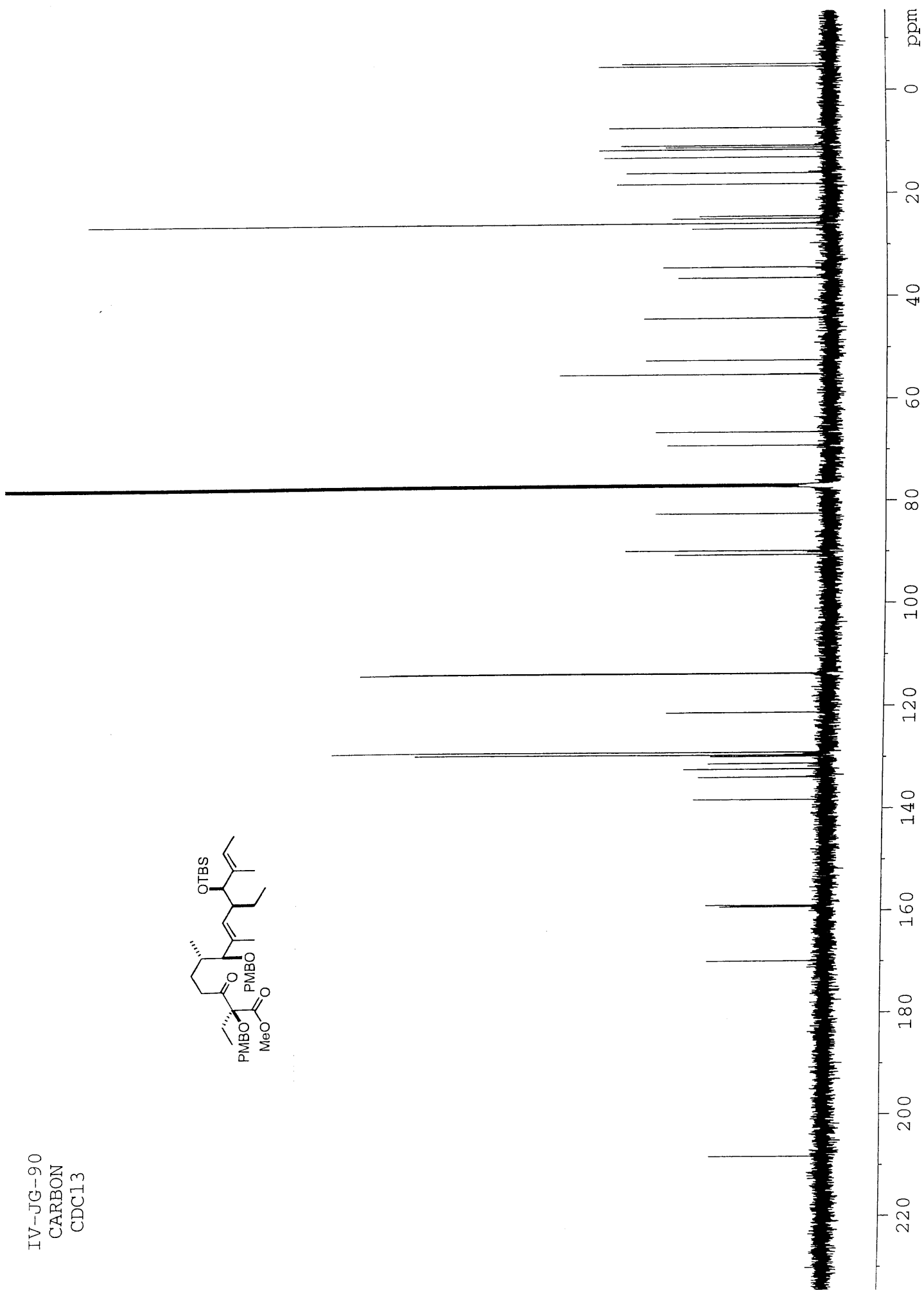
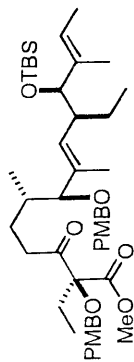


IV-JG-90  
PROTON  
CDCl3

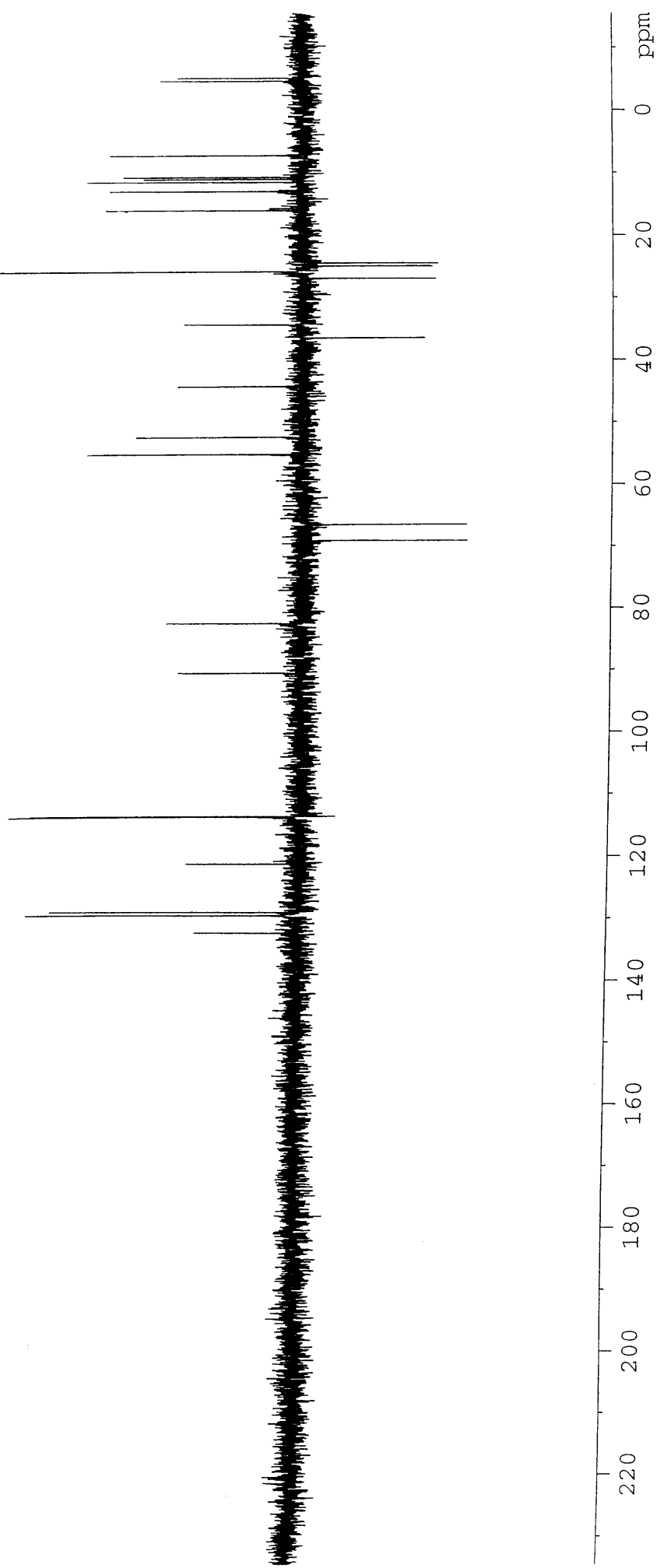
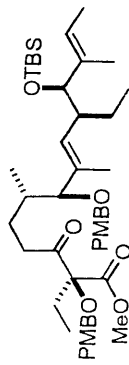




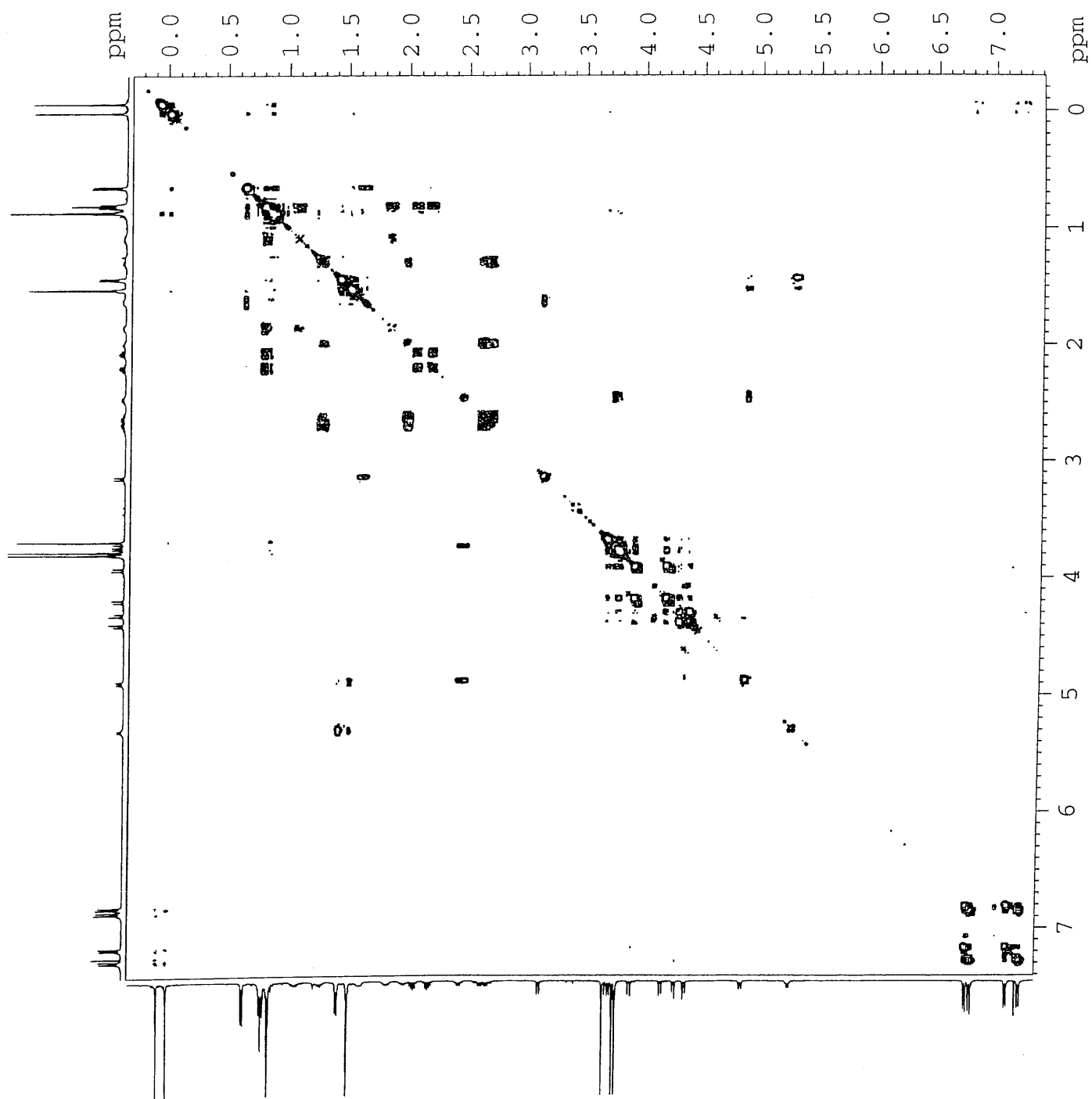
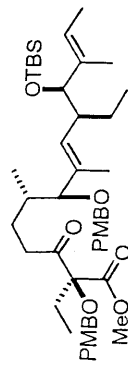
IV-JG-90  
CARBON  
CDCl<sub>3</sub>



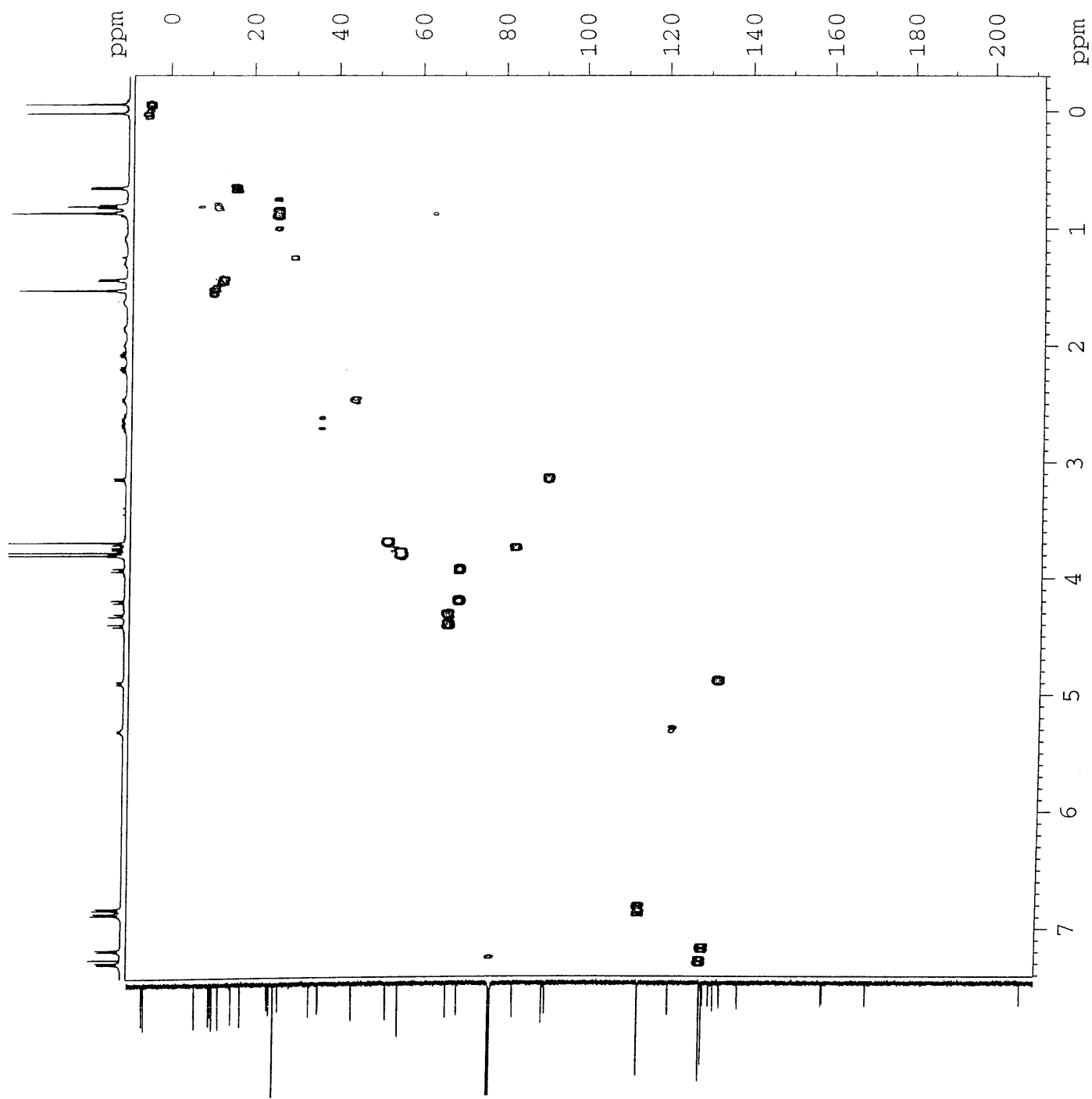
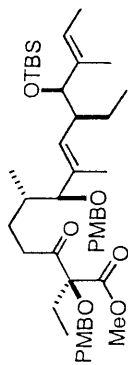
IV-JG-90  
DEPT  
CDCl<sub>3</sub>

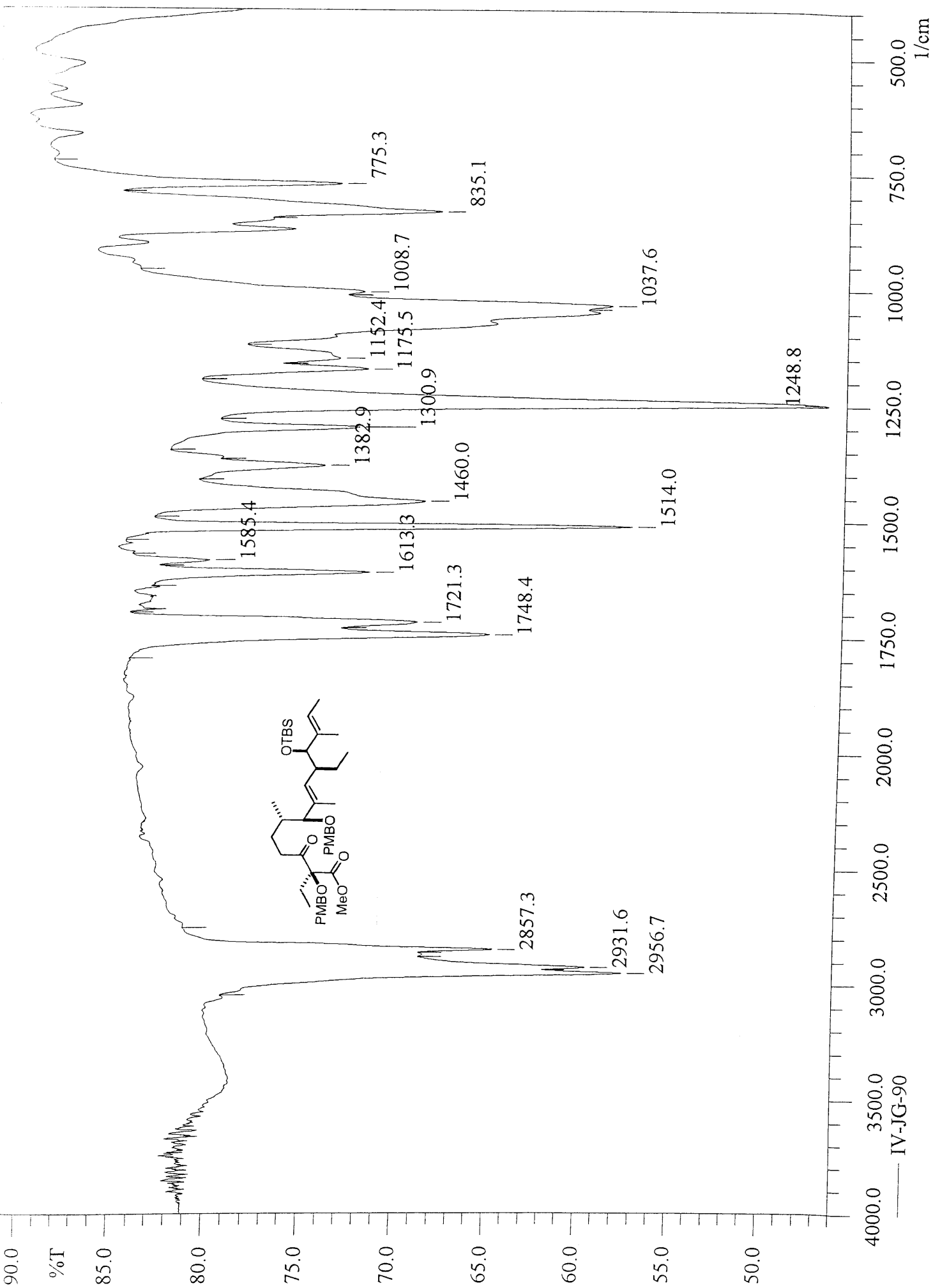


CDCL3

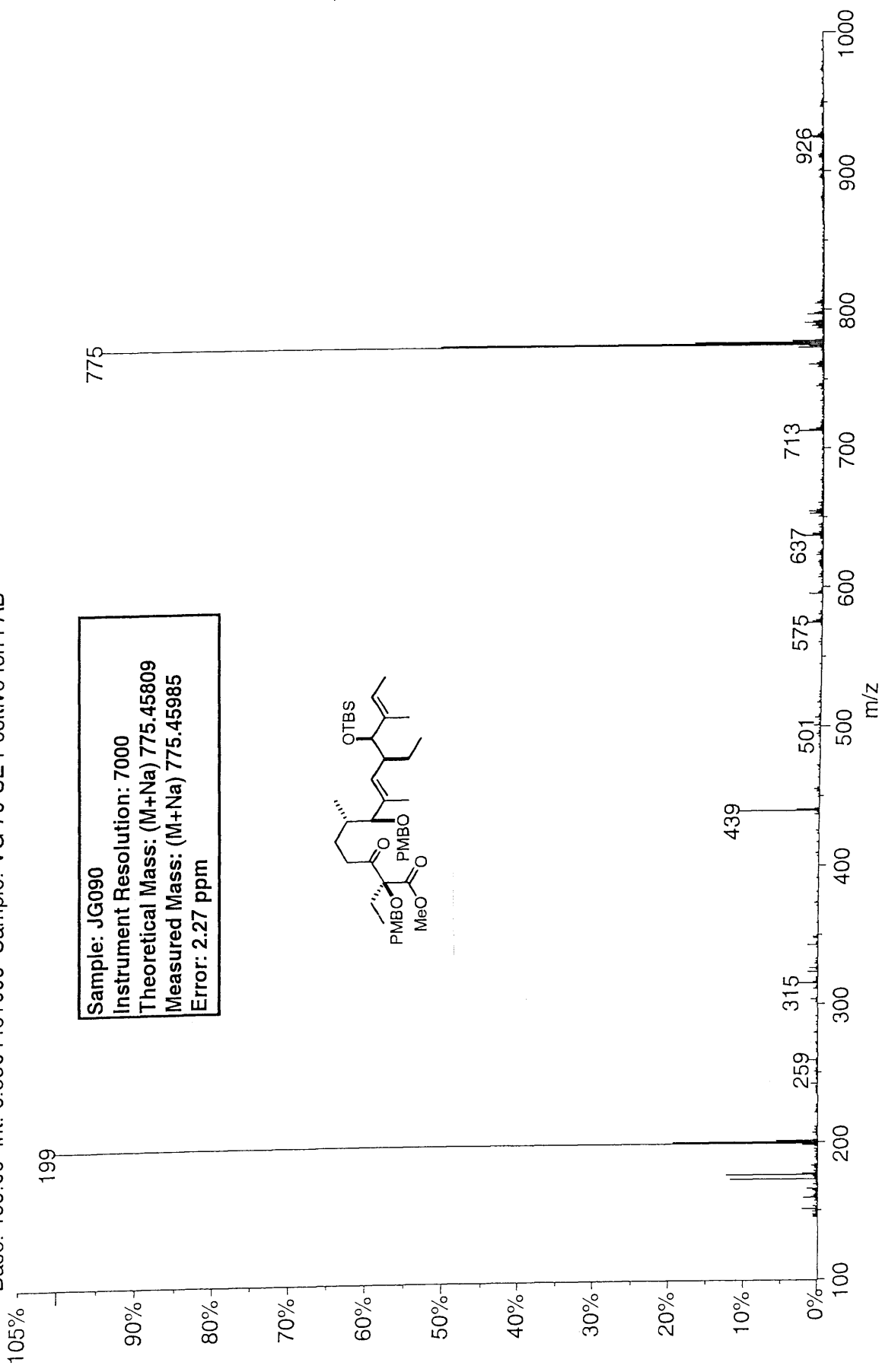


IV-JG-90  
HMQC  
CDC13

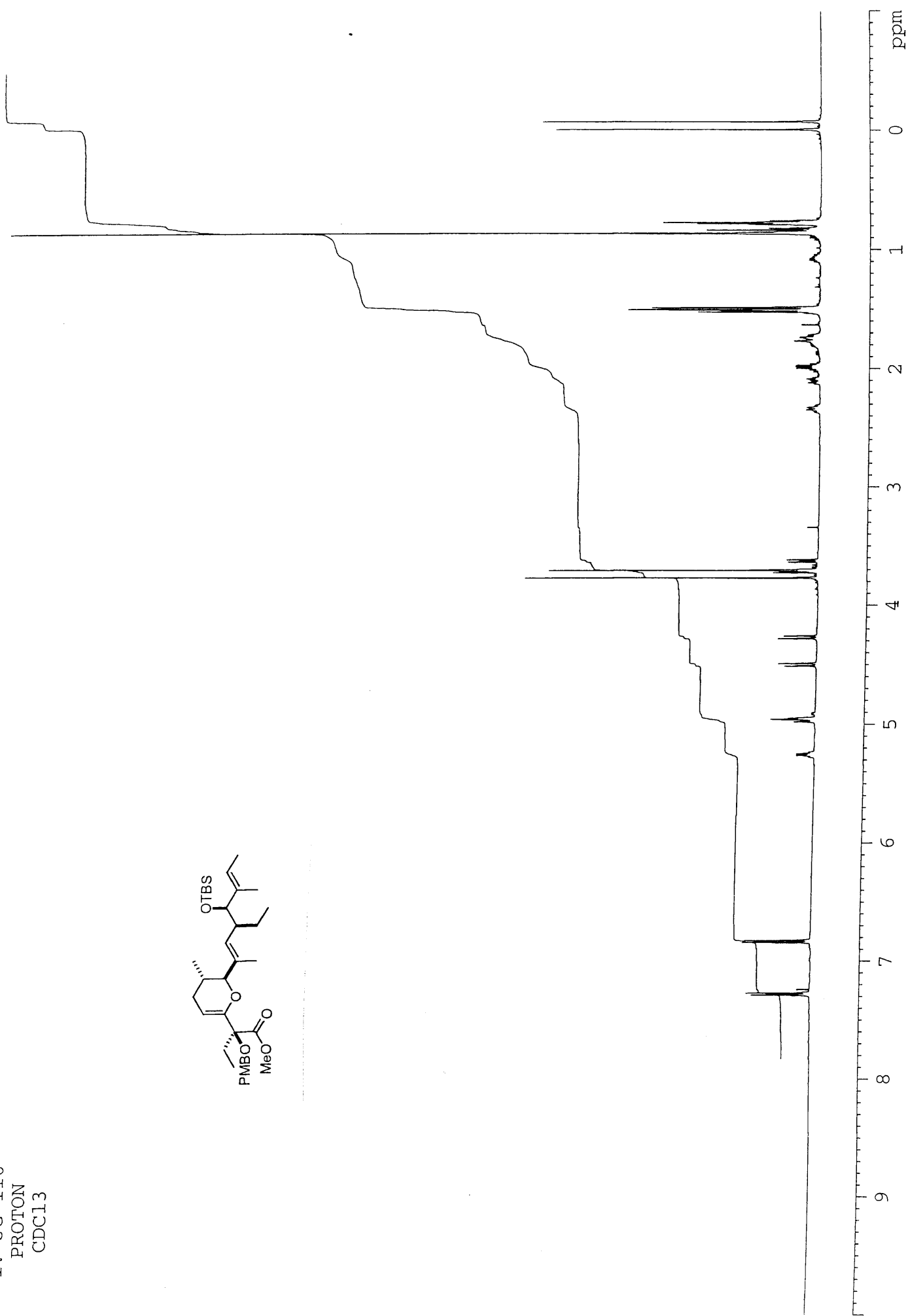
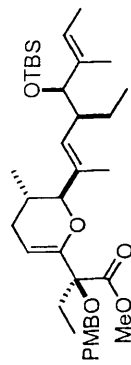




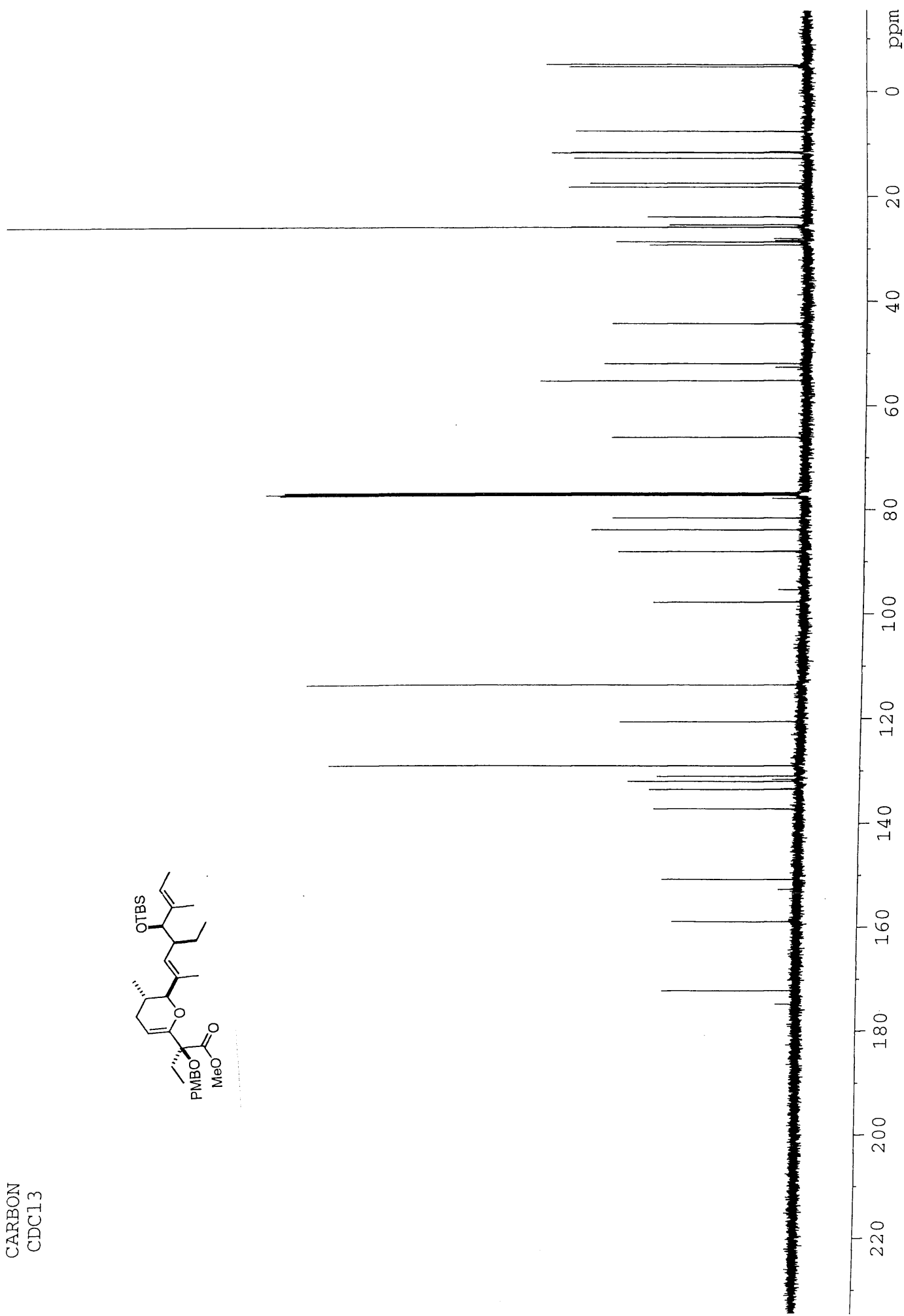
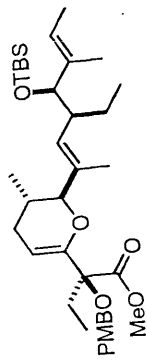
Base: 199.00 Int: 6.35044e+006 Sample: VG 70-SE Positive Ion FAB



IV-JG-110  
PROTON  
CDCl<sub>3</sub>

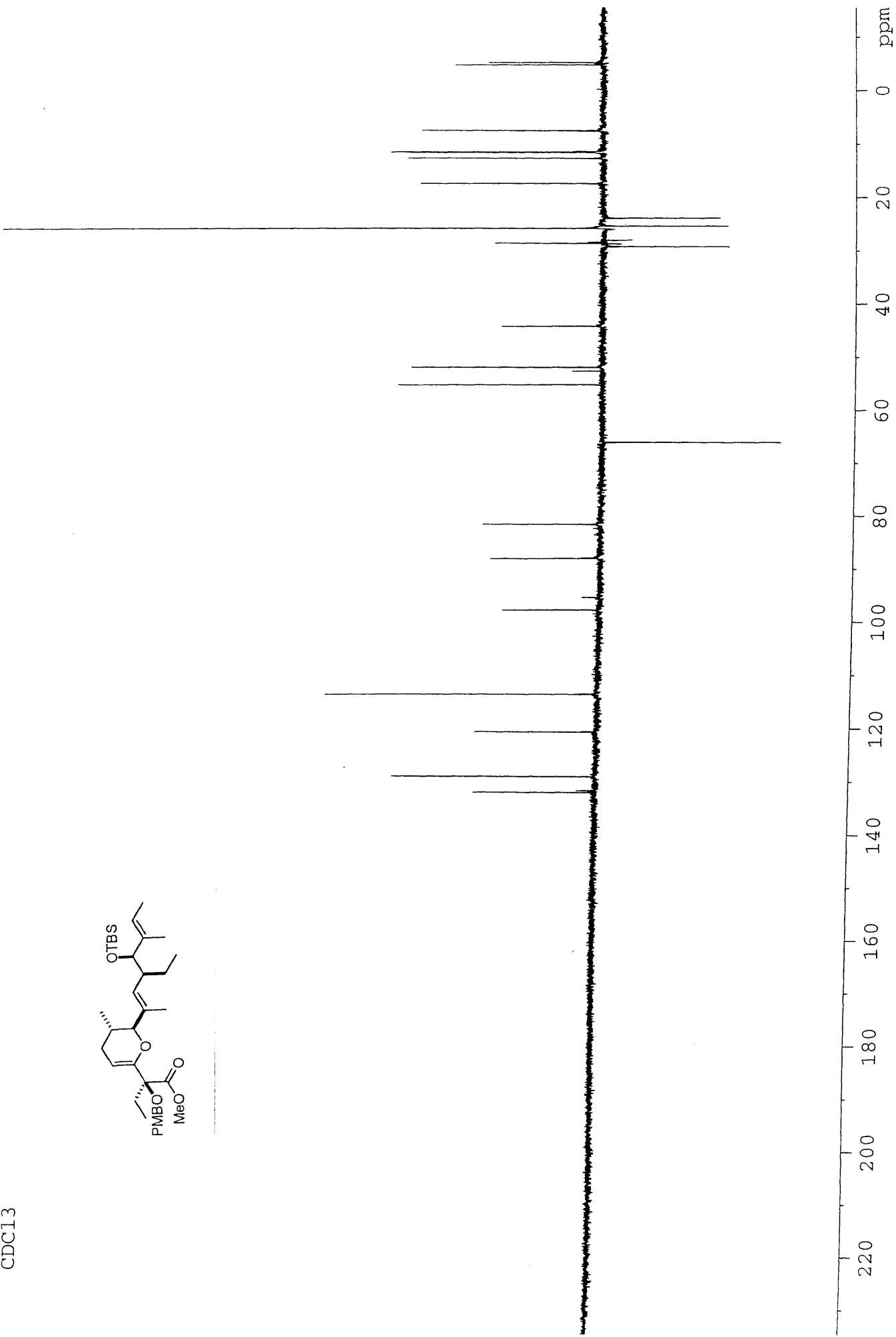
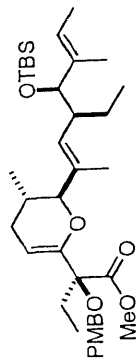


IV-JG-110  
CARBON  
CDCl<sub>3</sub>

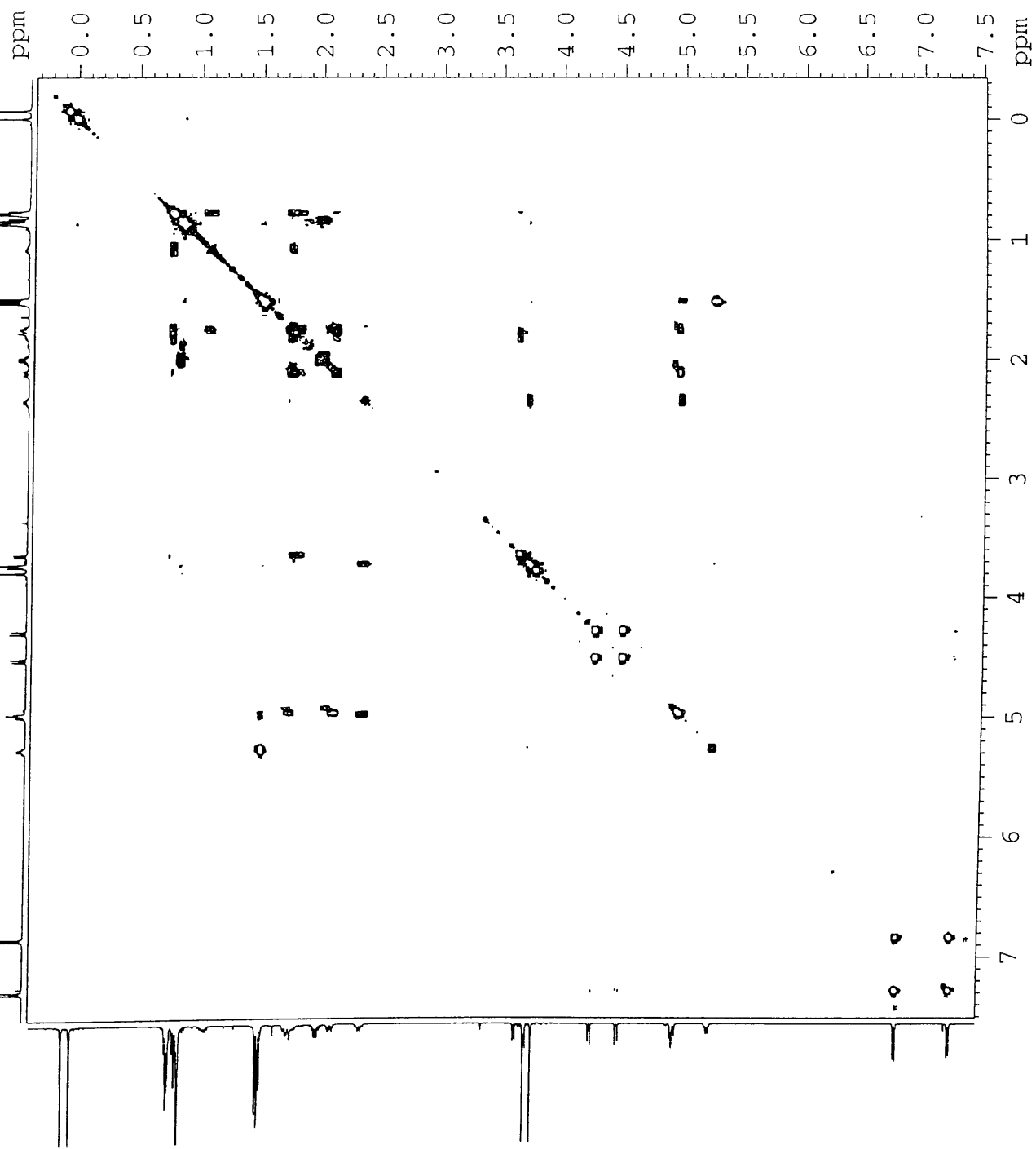
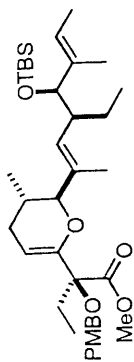




IV-JG-110  
DEPT  
CDCl<sub>3</sub>



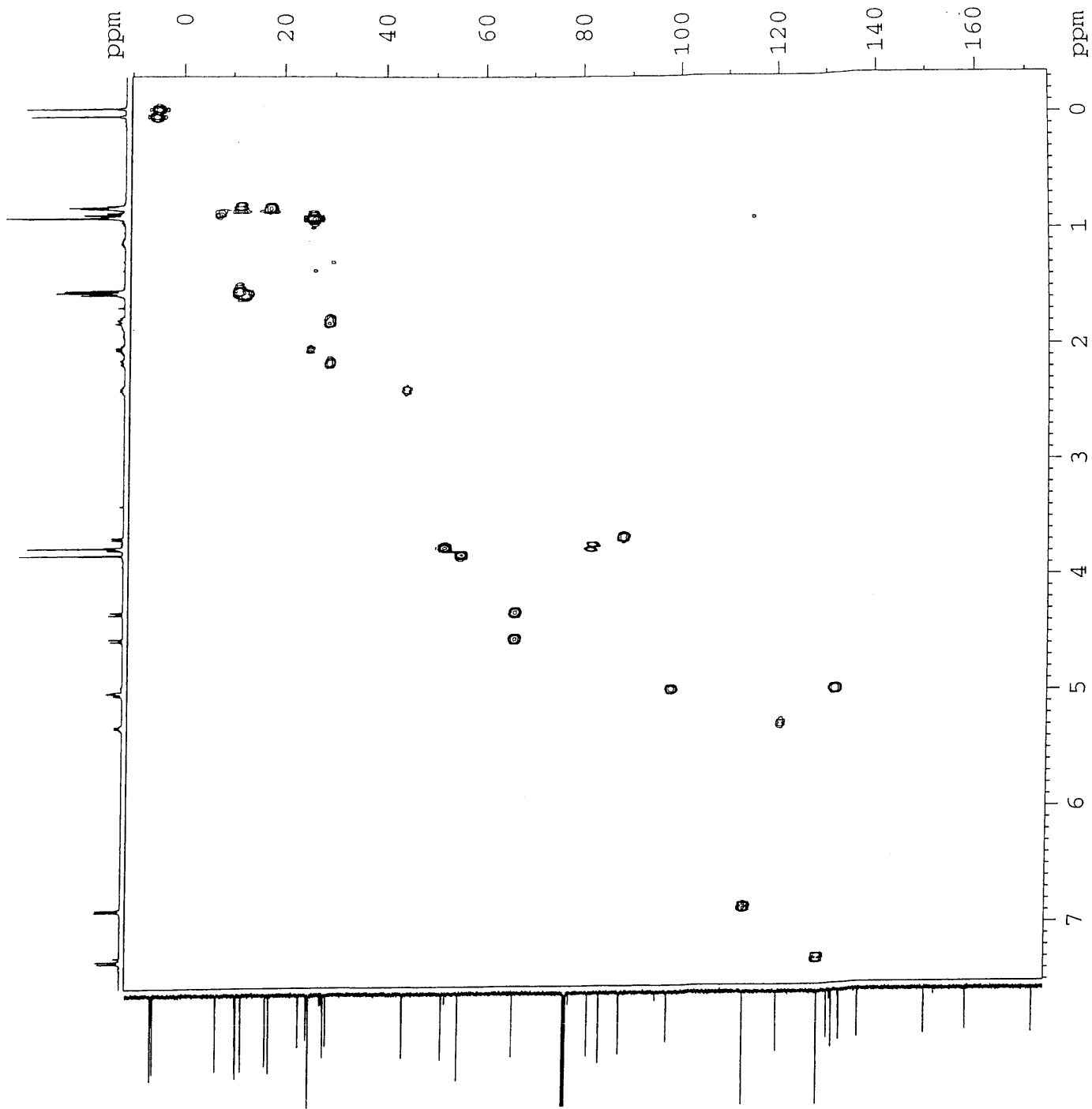
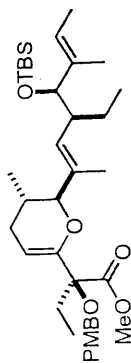
CDC13

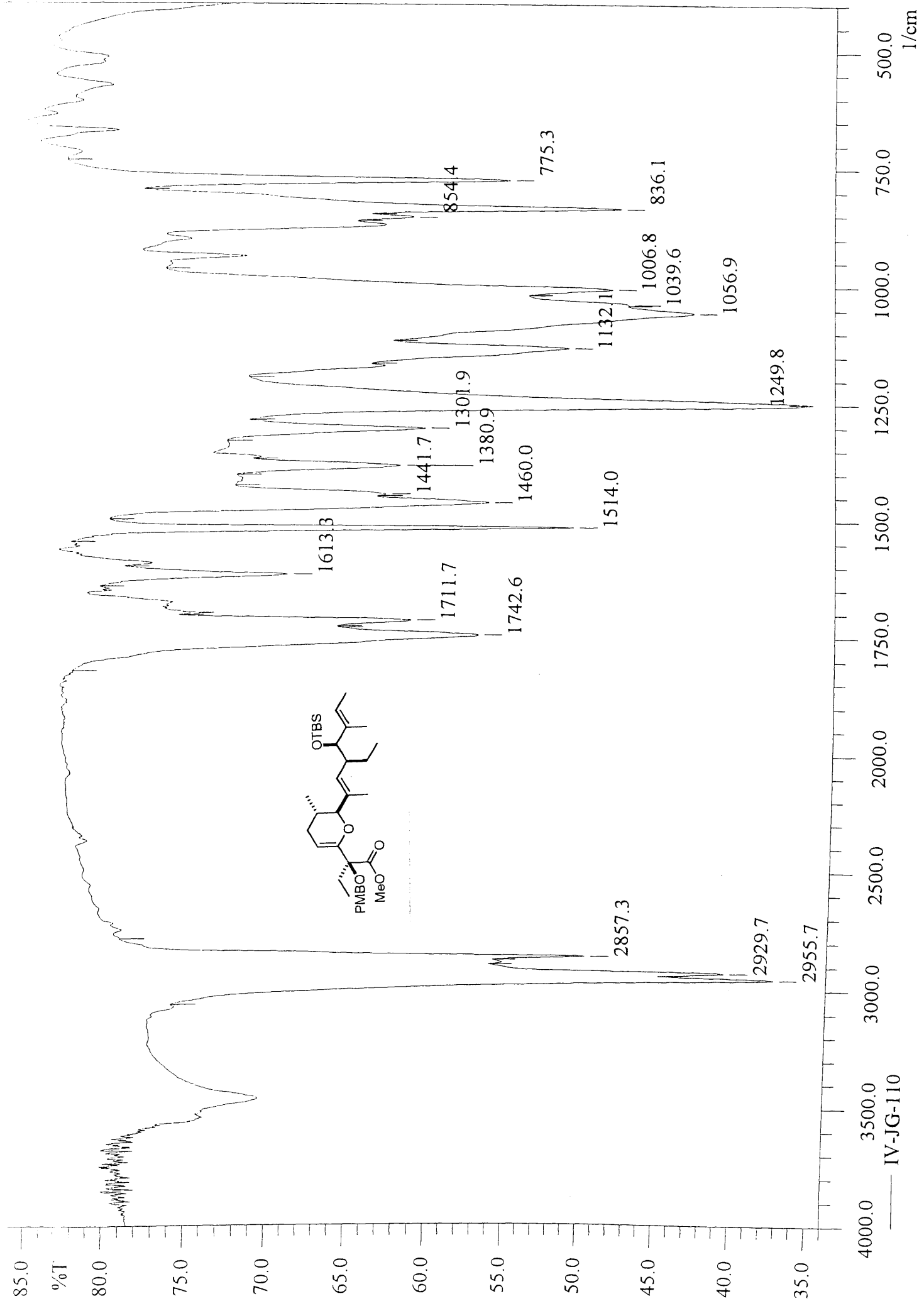


IV-JG-110

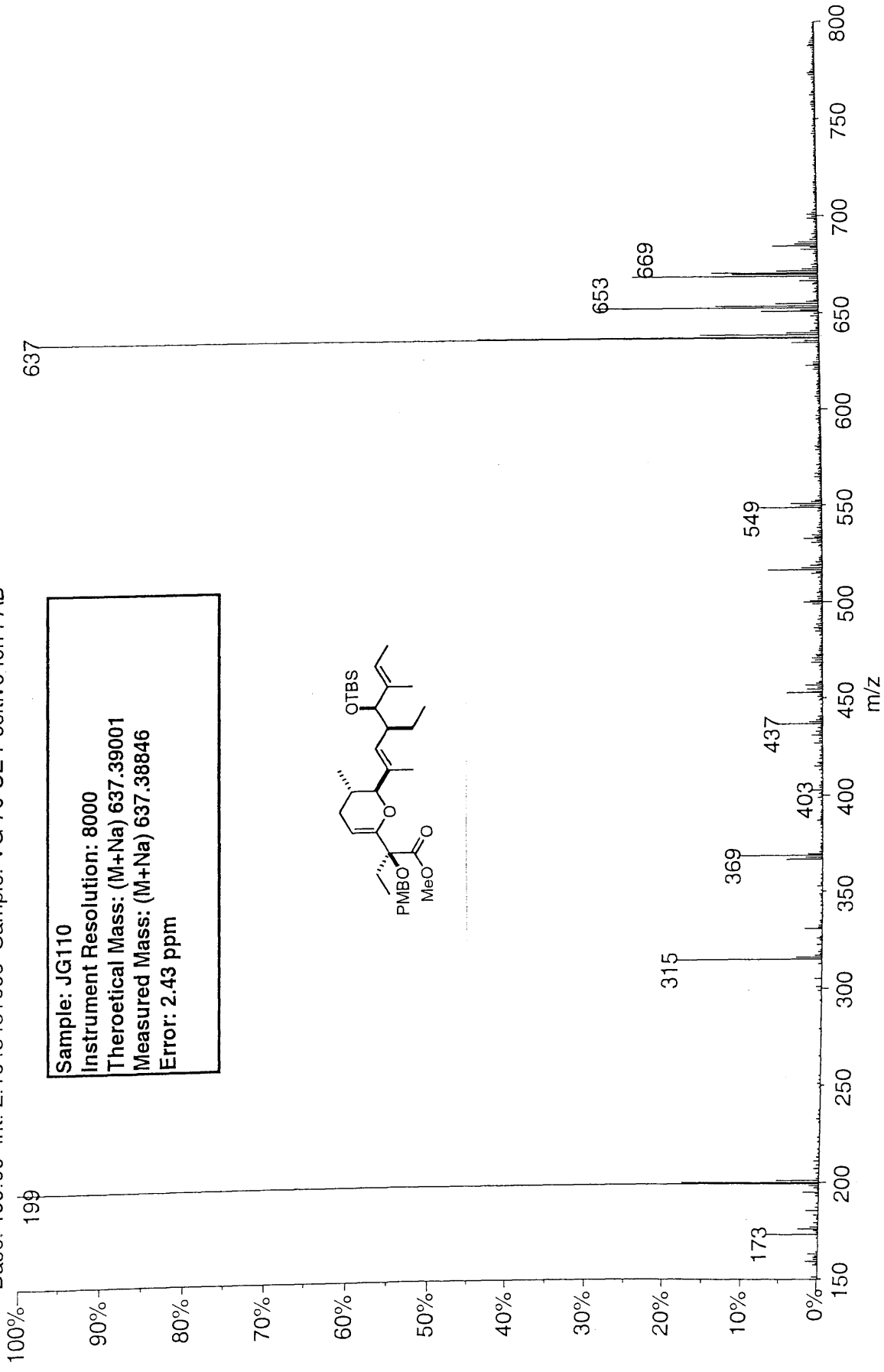
HMQC

CDC13

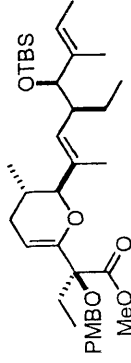




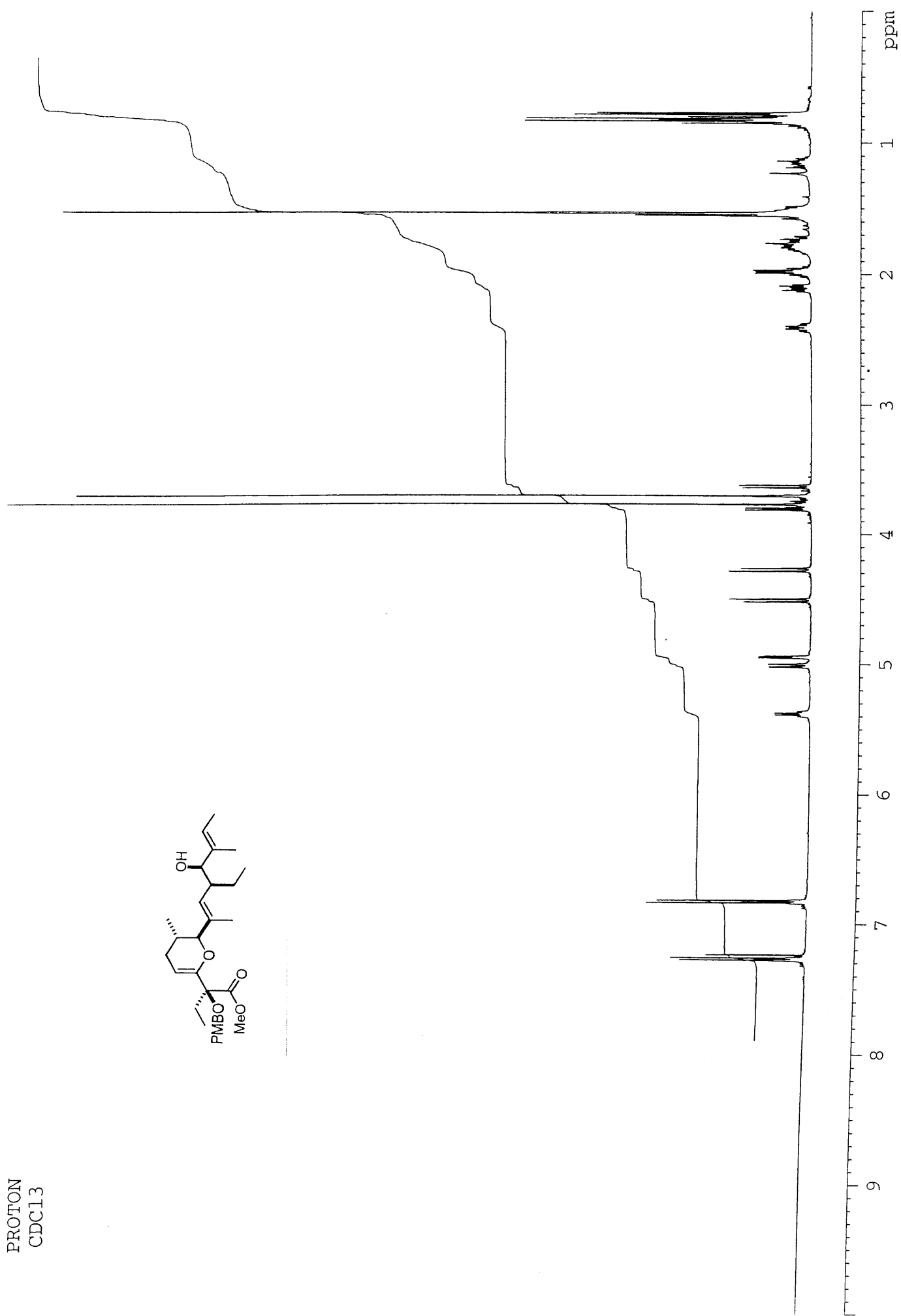
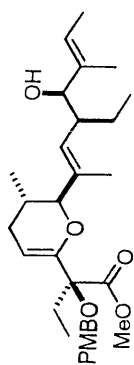
01090606: Scan Avg 96-98 (17.55 - 17.92 min) - Back  
Base: 199.00 Int: 2.10454e+006 Sample: VG 70-SE Positive Ion FAB



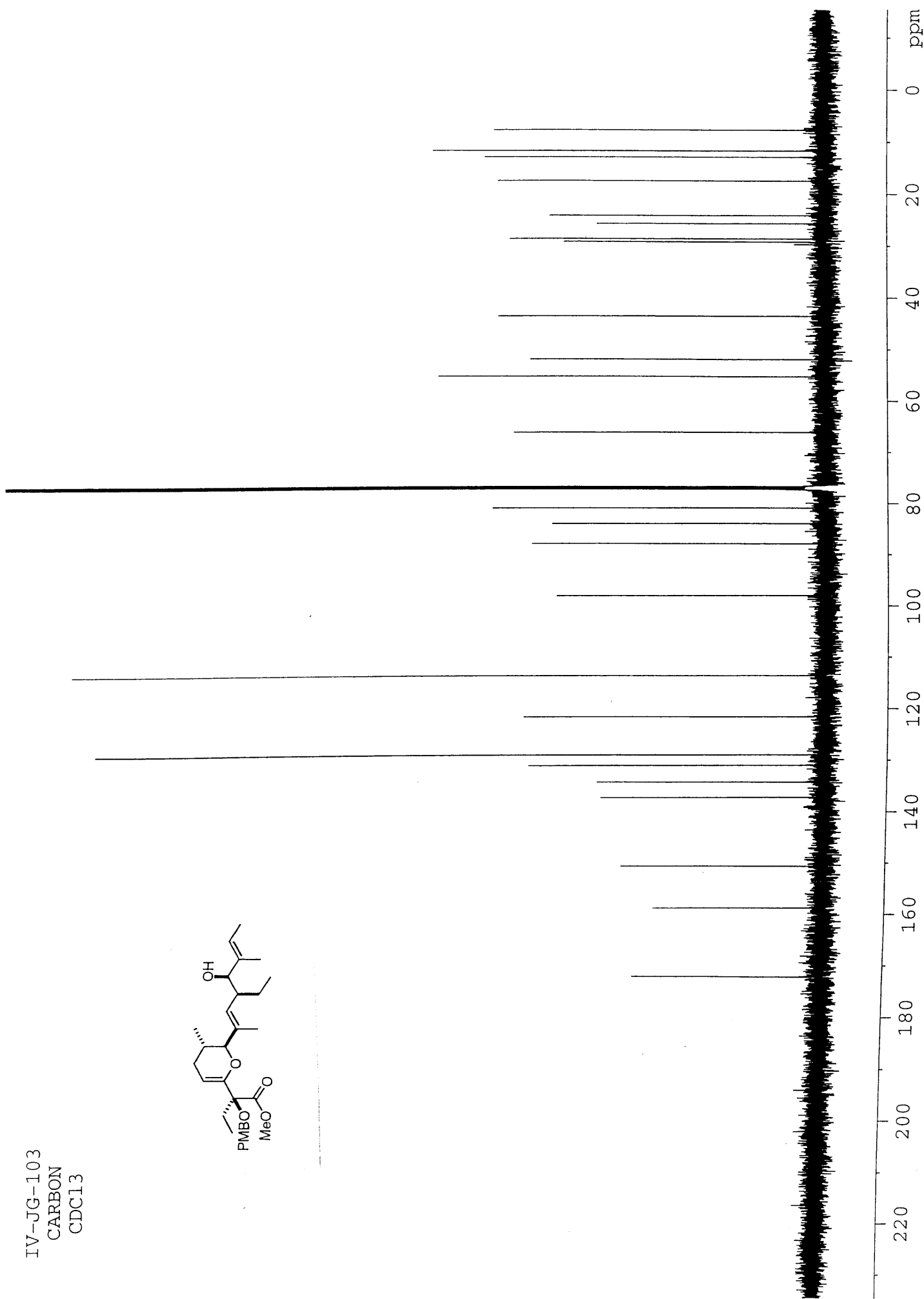
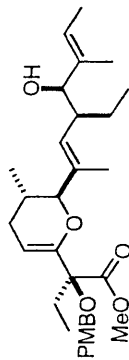
Sample: JG110  
Instrument Resolution: 8000  
Theoretical Mass: (M+Na) 637.39001  
Measured Mass: (M+Na) 637.38846  
Error: 2.43 ppm



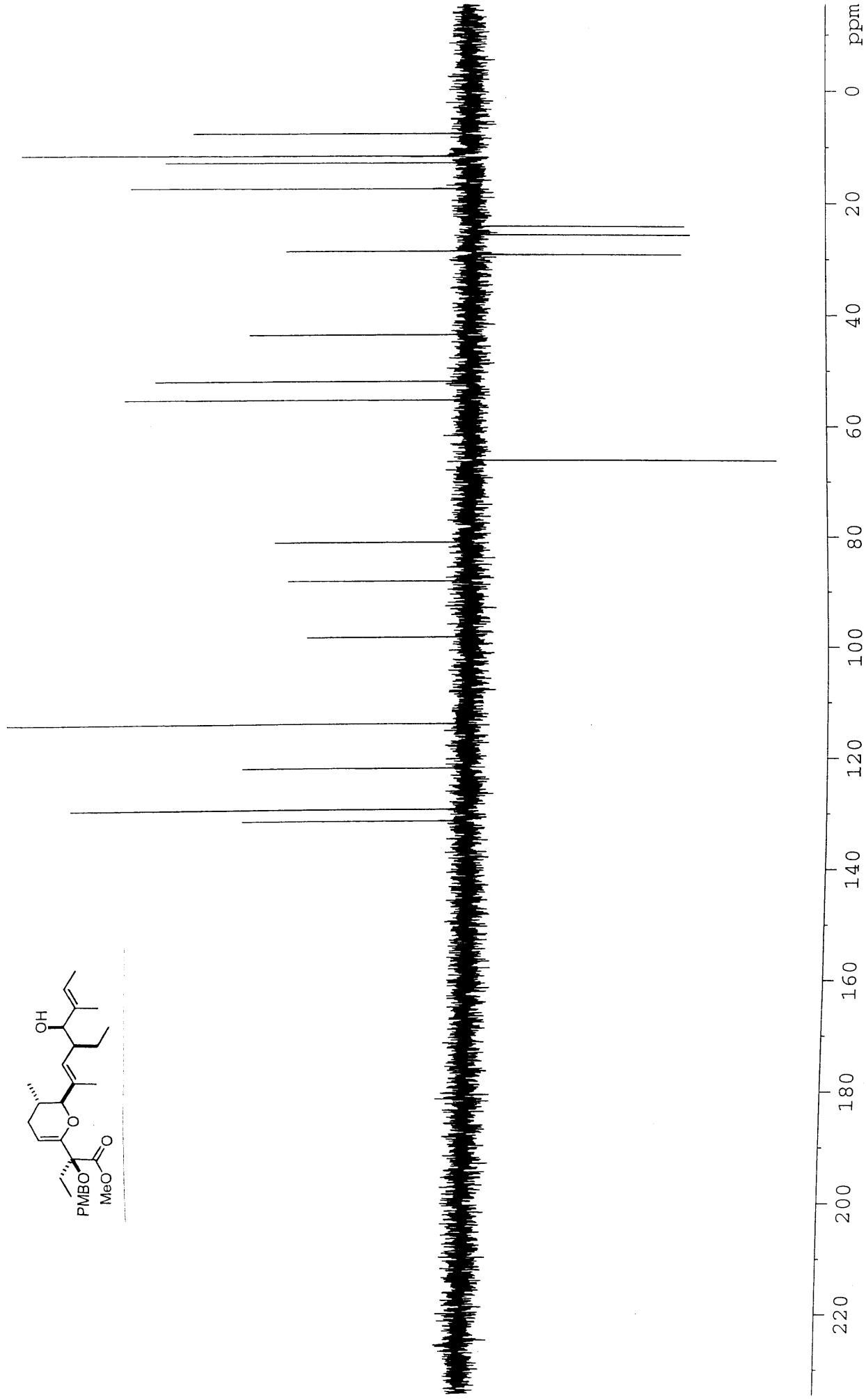
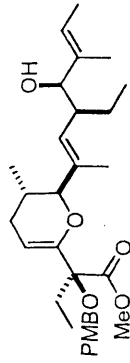
IV-JG-103  
PROTON  
CDCl<sub>3</sub>



IV-JG-103  
CARBON  
CDCl<sub>3</sub>

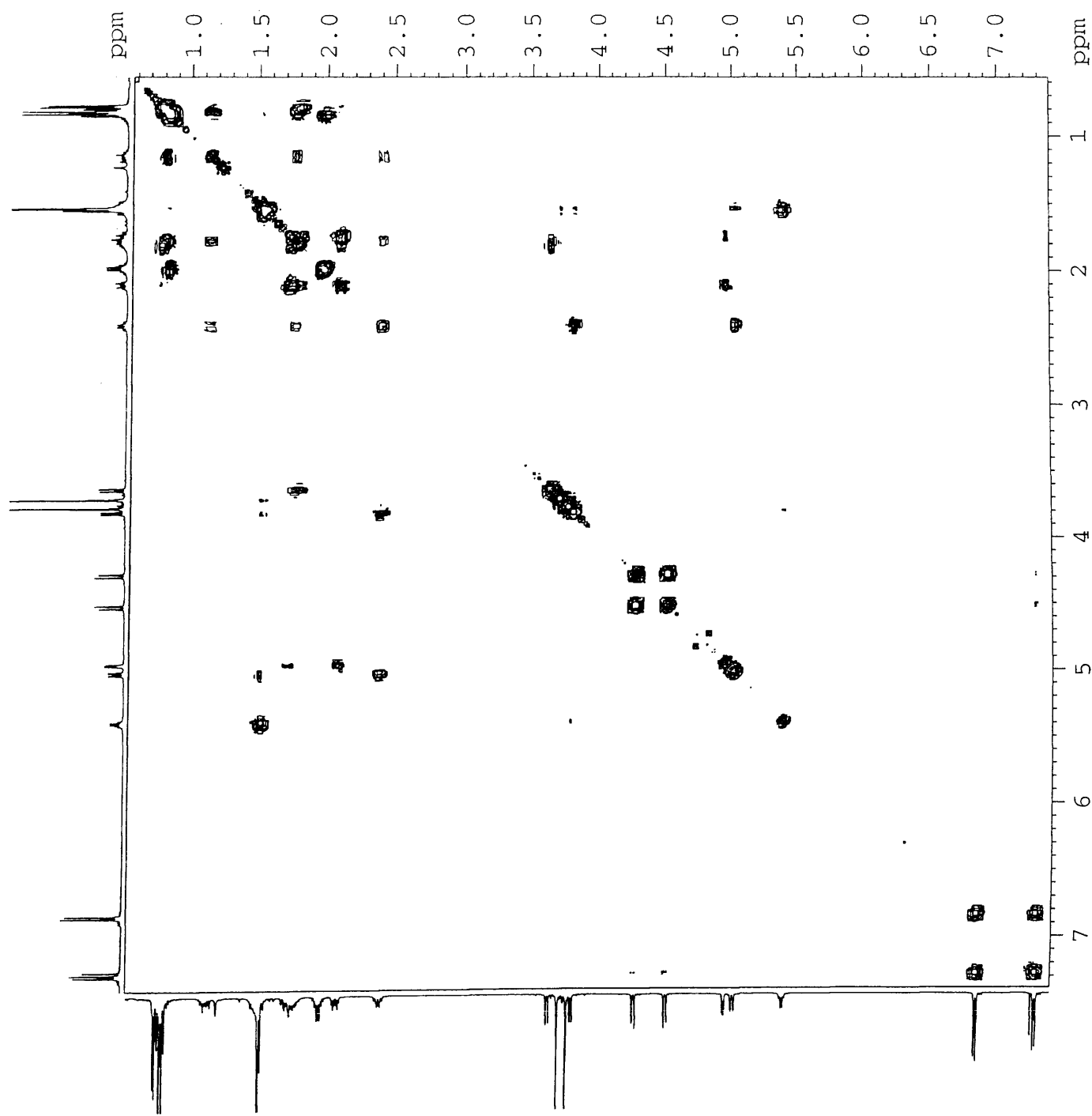
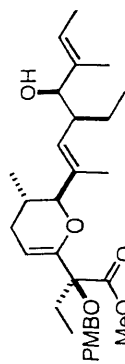


IV-JG-103  
DEPT  
CDCl<sub>3</sub>

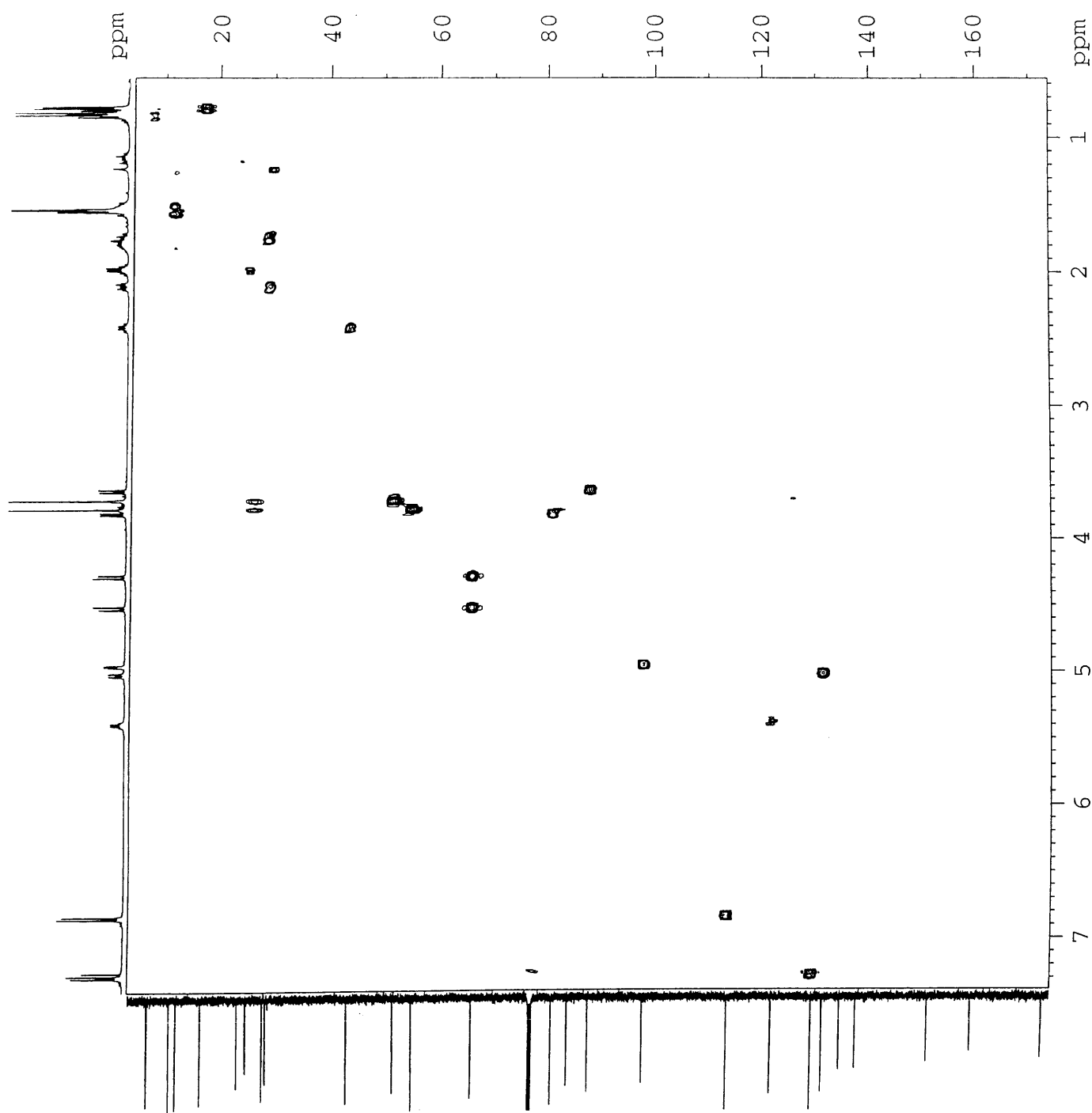
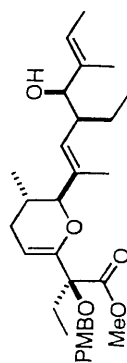


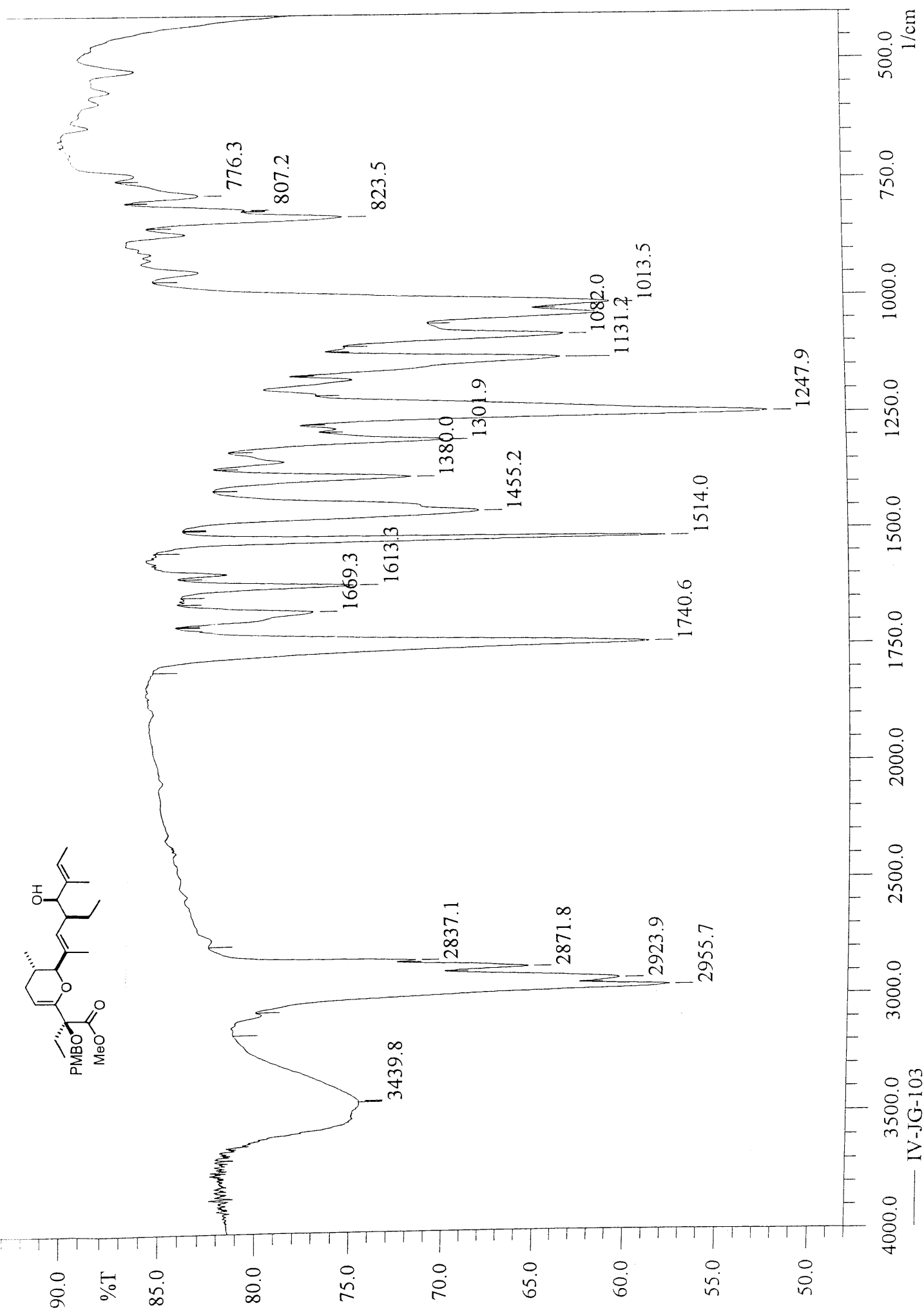
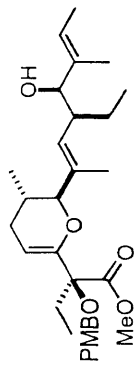


IV-JG-103  
COSY  
CDCl<sub>3</sub>



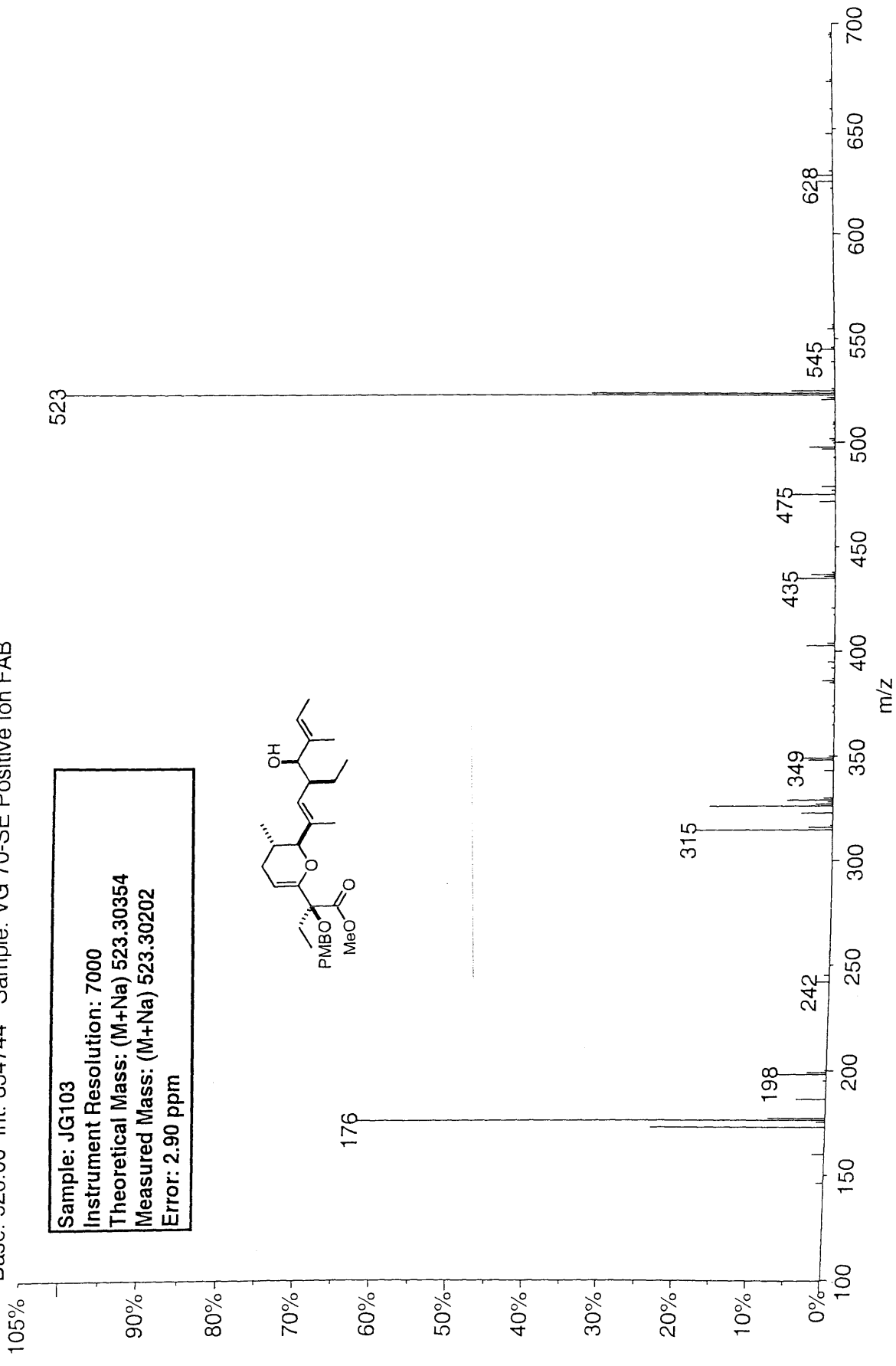
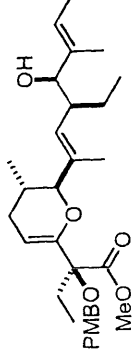
IV-JG-103  
HMQC  
CDCl<sub>3</sub>



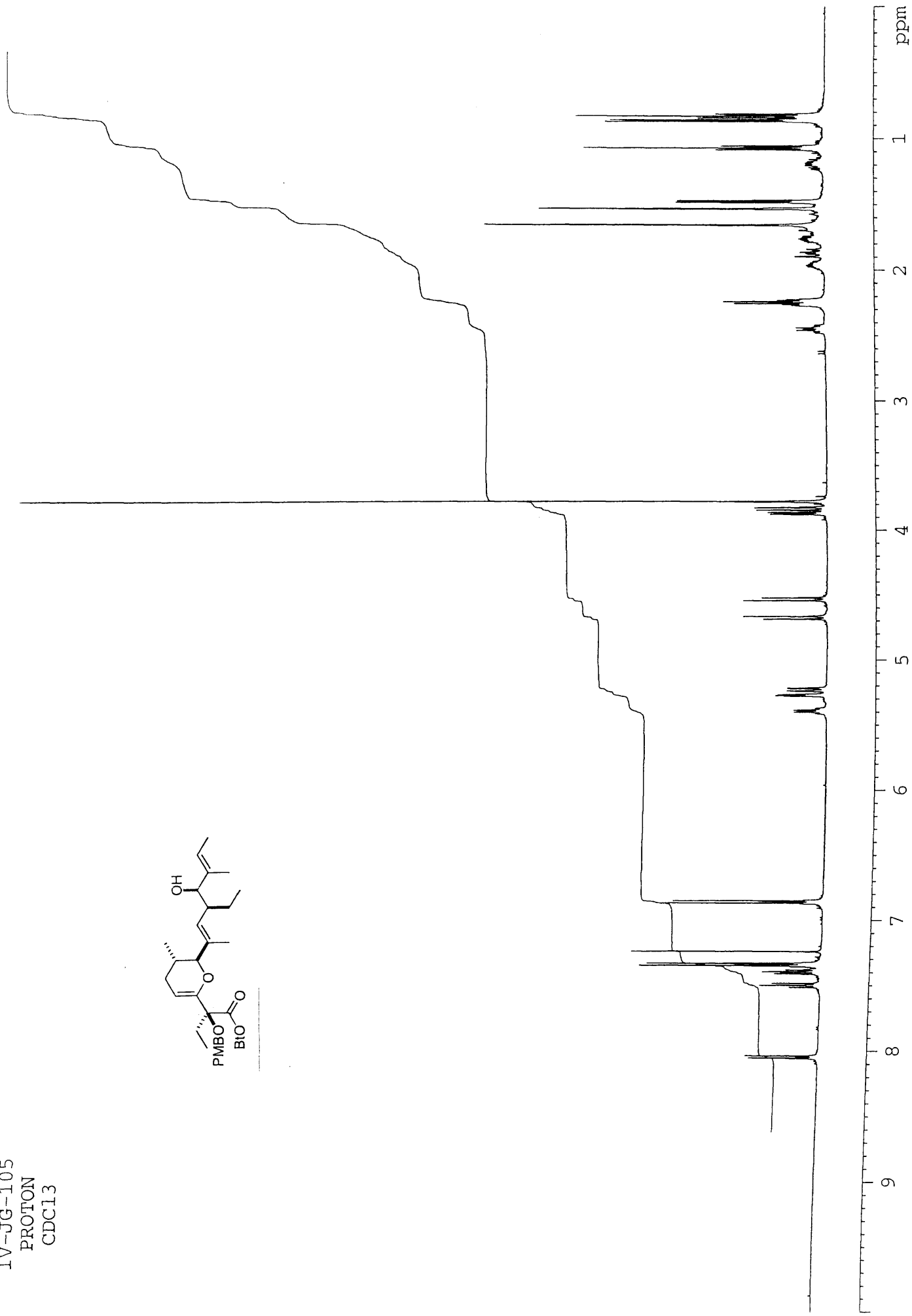
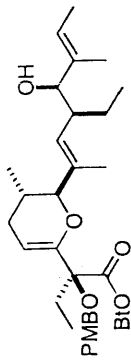


01270206: Scan 258 (47.25 min) - Back  
Base: 523.00 Int: 834744 Sample: VG 70-SE Positive Ion FAB

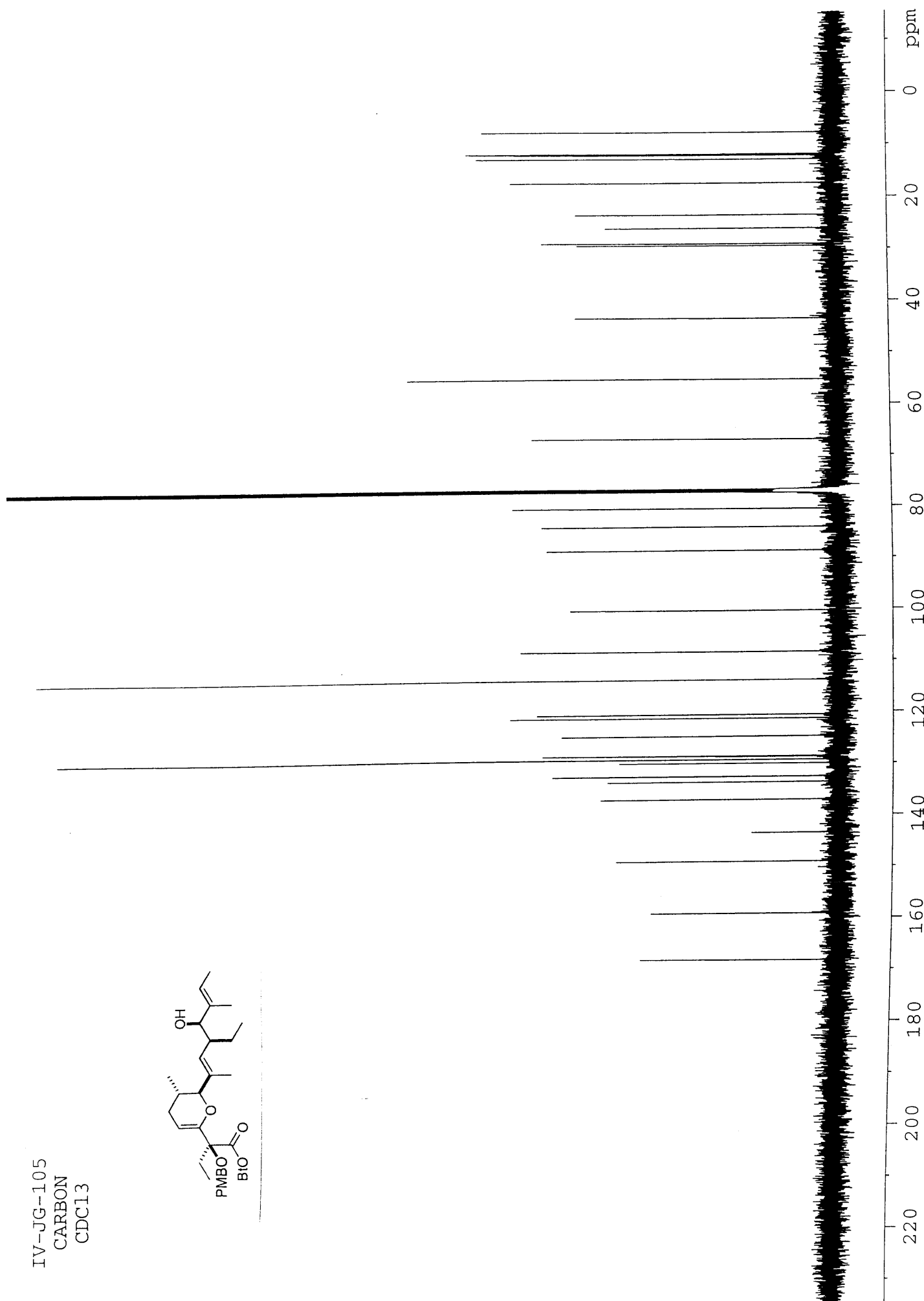
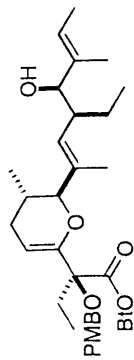
Sample: JG103  
Instrument Resolution: 7000  
Theoretical Mass: (M+Na) 523.30354  
Measured Mass: (M+Na) 523.30202  
Error: 2.90 ppm



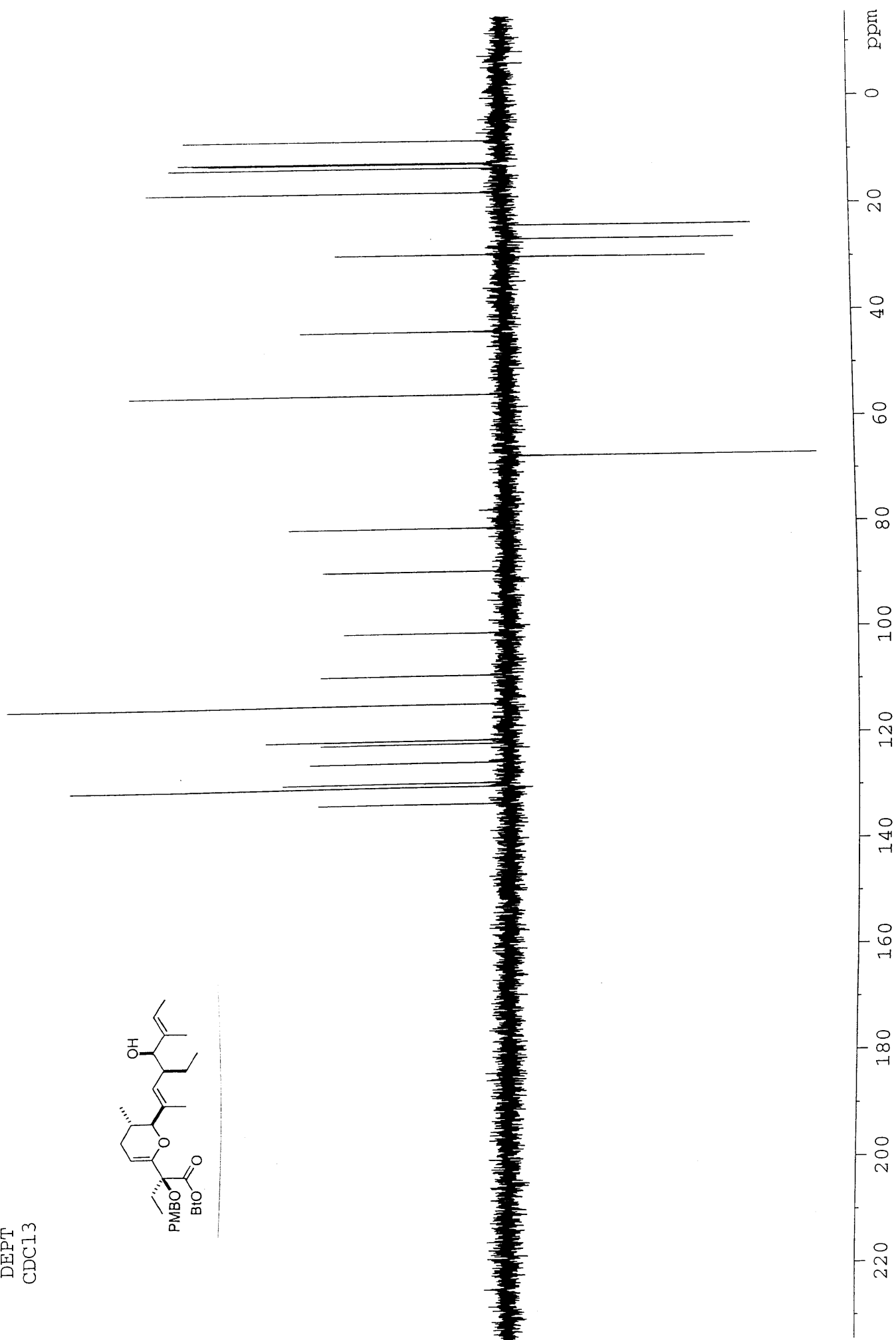
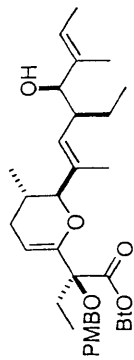
IV-JG-105  
PROTON  
CDCl<sub>3</sub>

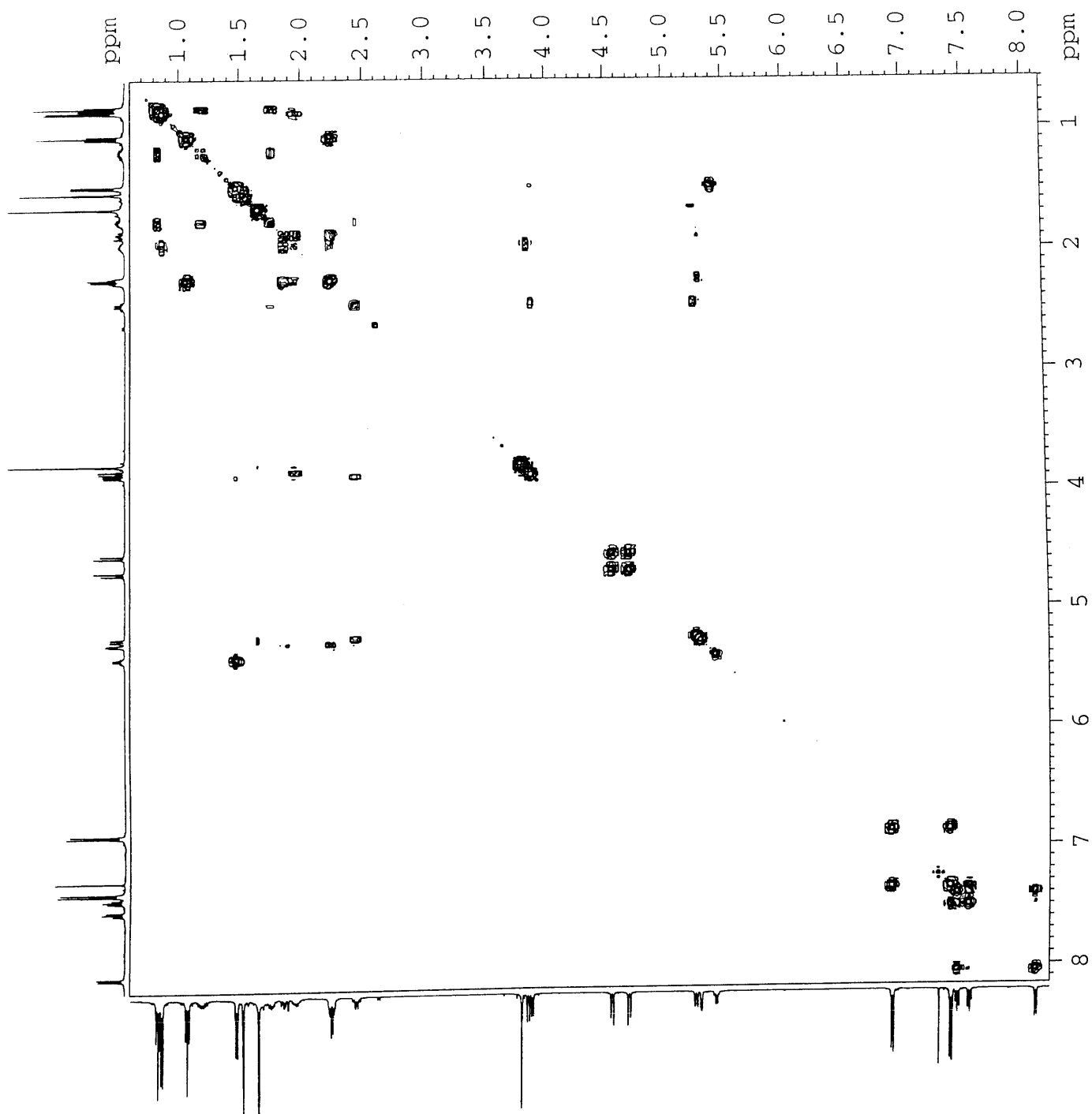
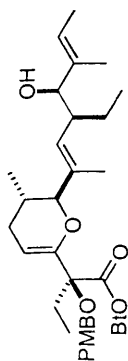


IV-JG-105  
CARBON  
CDCl<sub>3</sub>



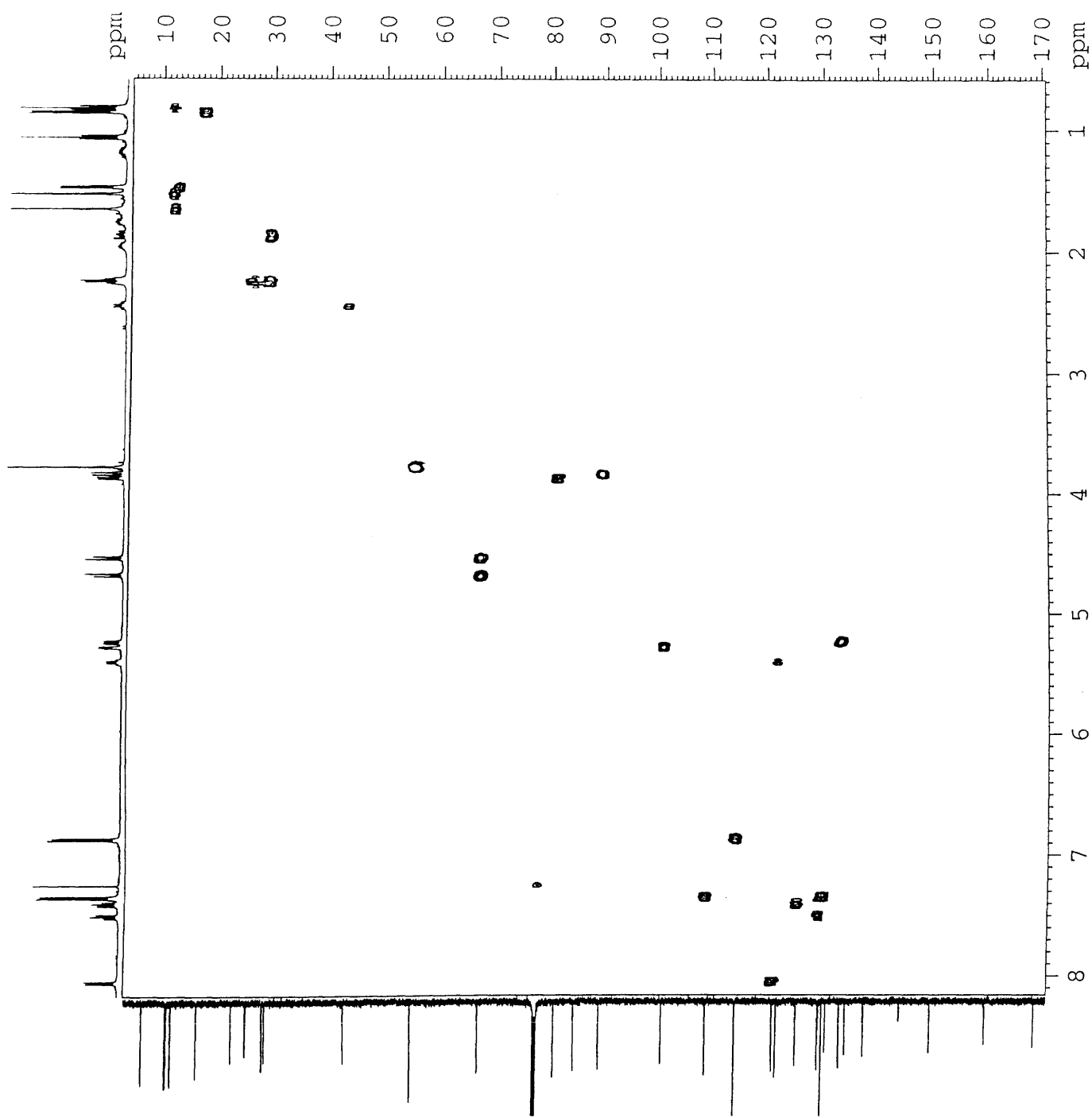
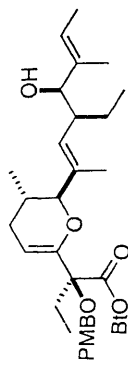
IV-JG-105  
DEPT  
CDCl<sub>3</sub>

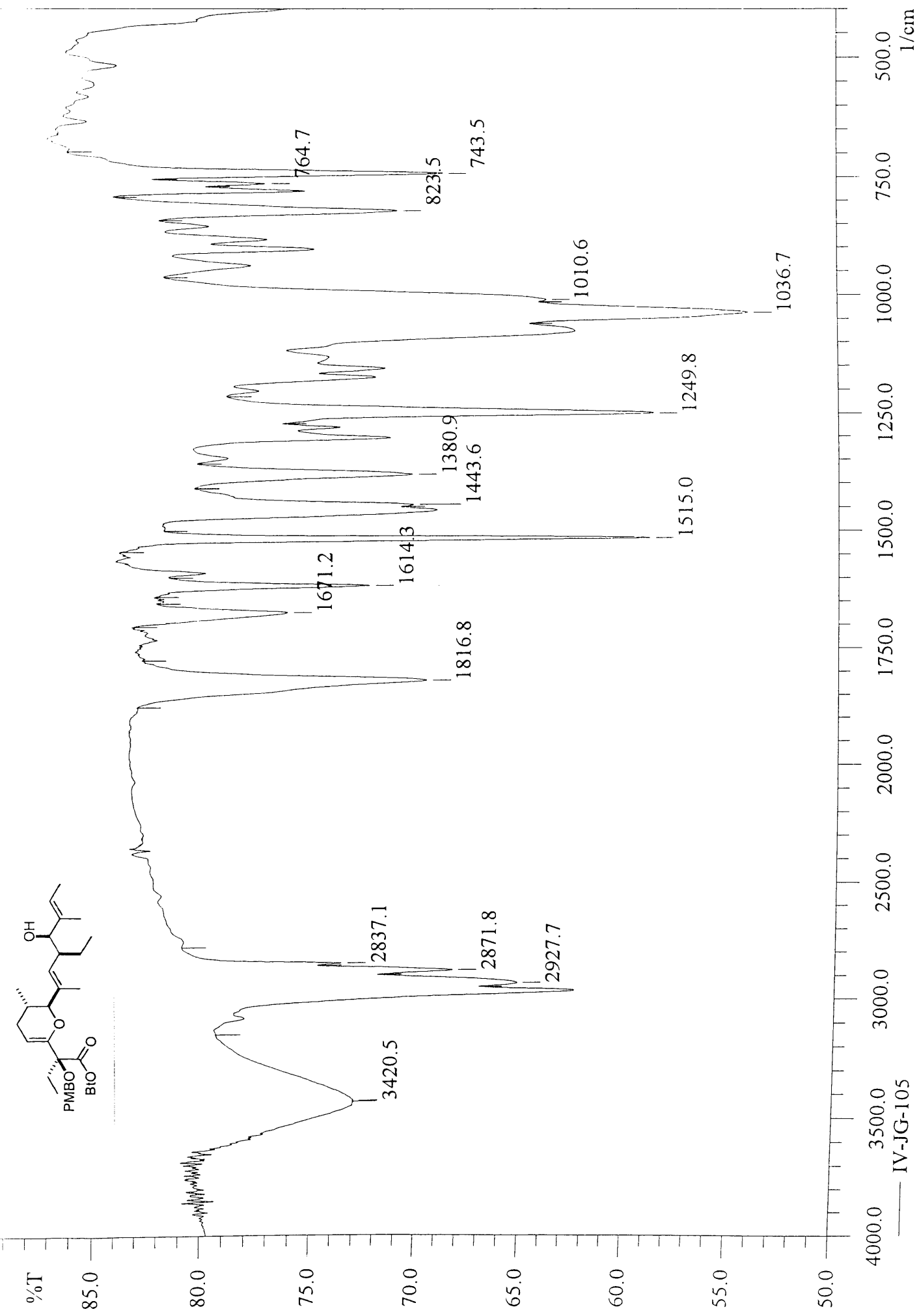


COSY  
CDC13



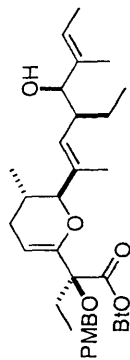
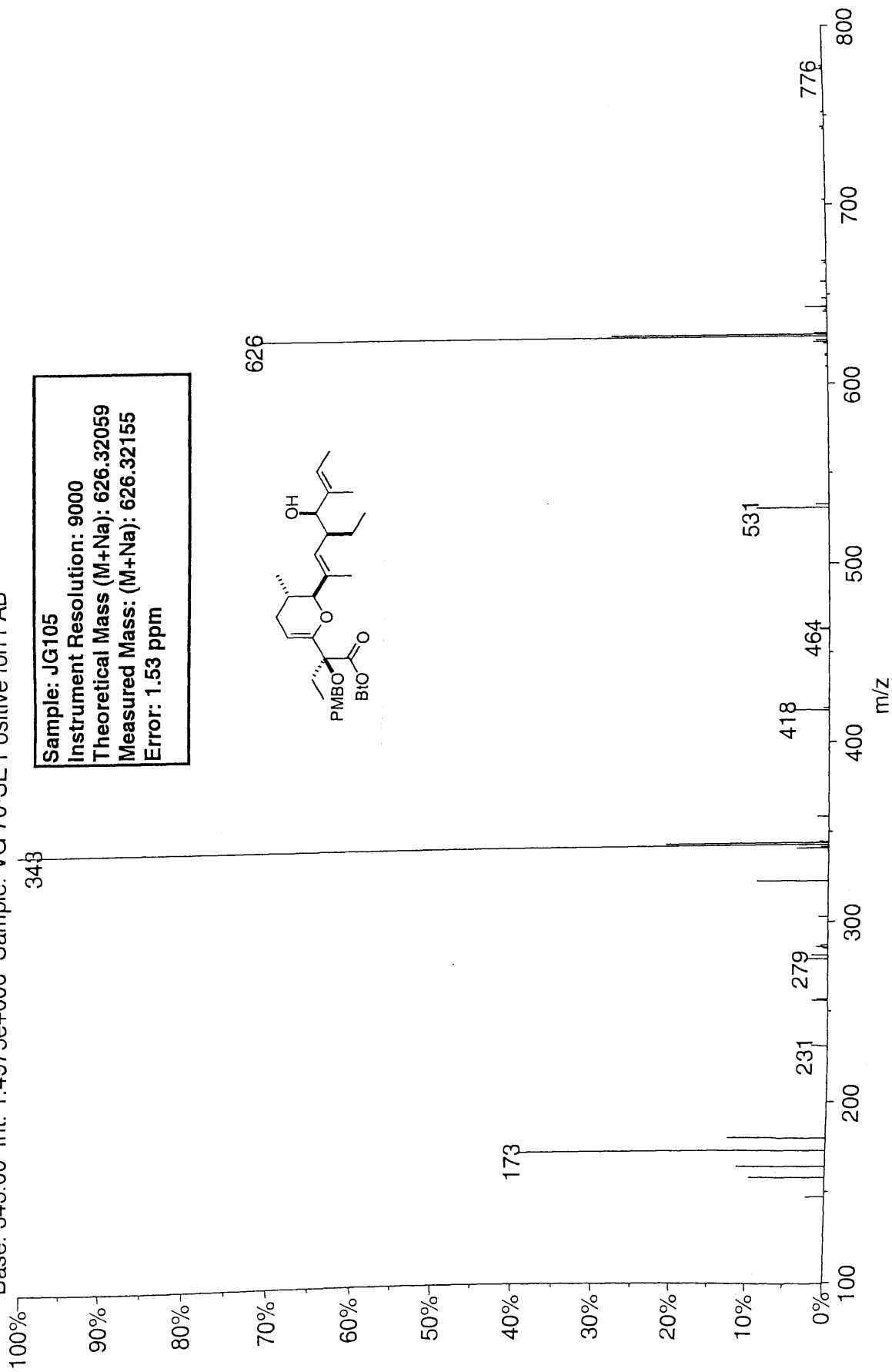
IV-JG-105  
HMQC  
CDCl<sub>3</sub>



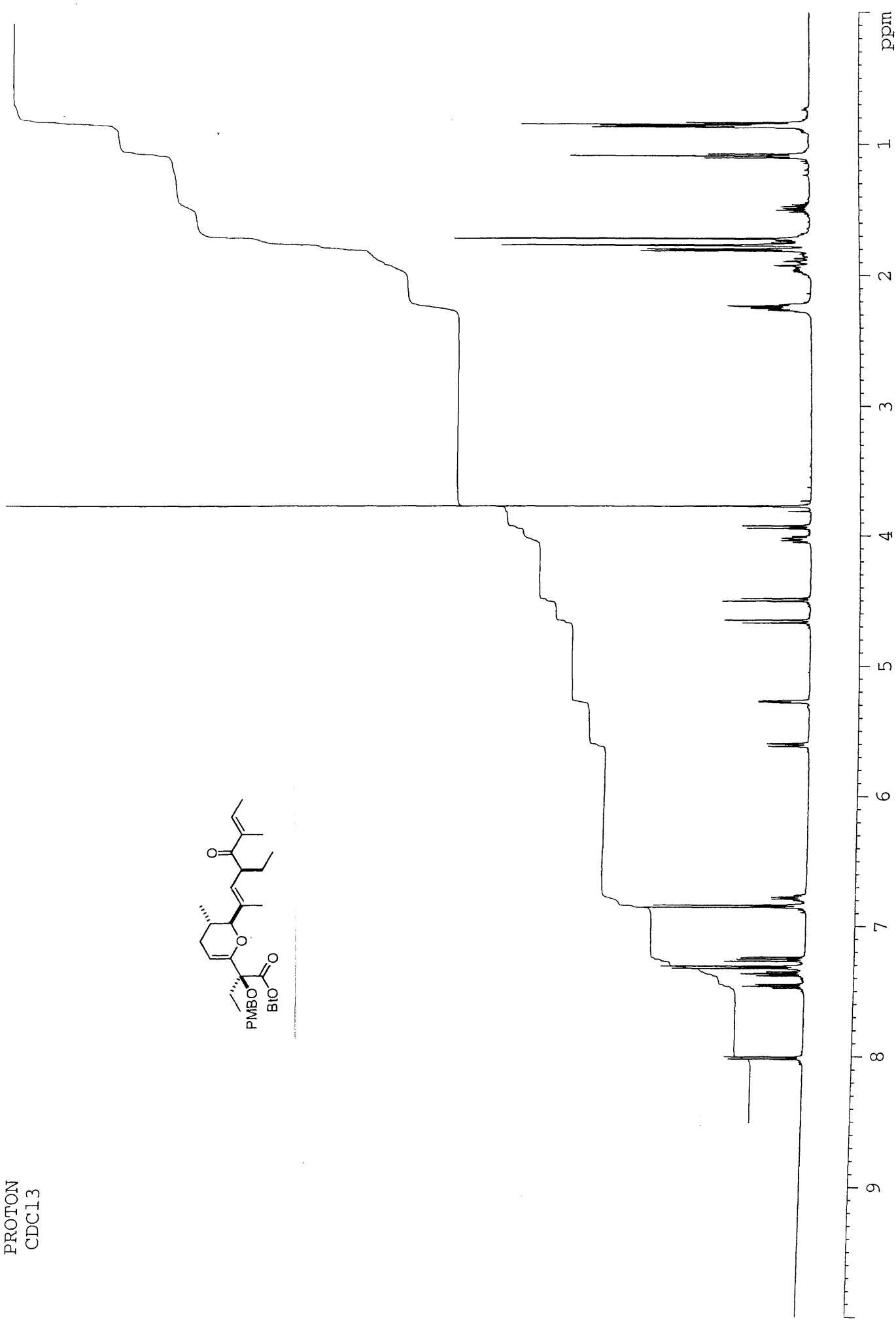
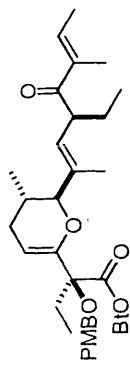


03080306: Scan Avg 189-191 (34.60 - 34.97 min) - Back  
Base: 343.00 Int: 1.4975e+006 Sample: VG 70-SE Positive Ion FAB

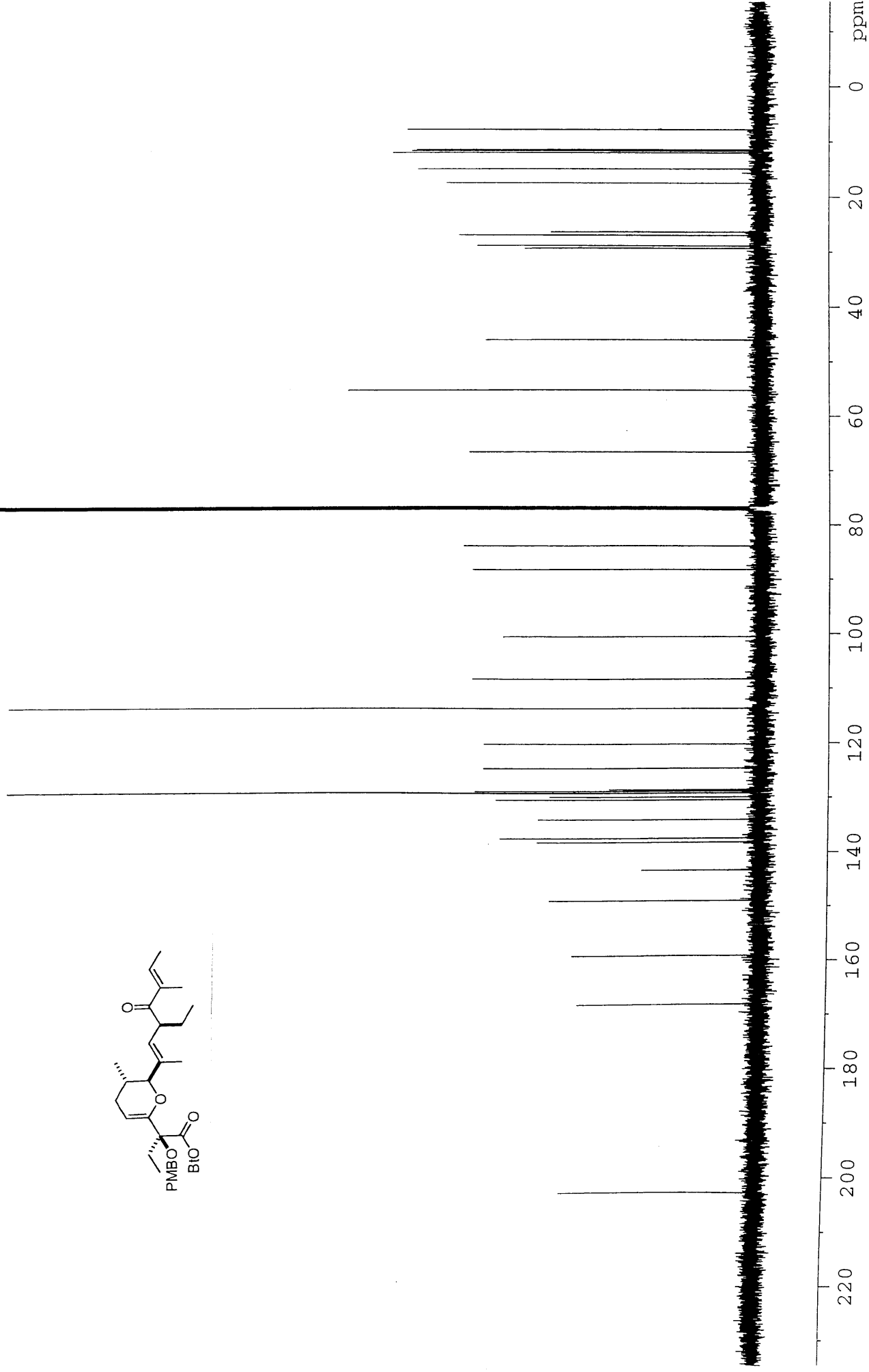
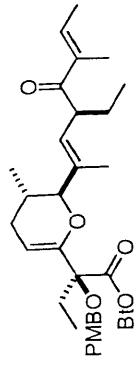
Sample: JG105  
Instrument Resolution: 9000  
Theoretical Mass (M+Na): 626.32059  
Measured Mass: (M+Na): 626.32155  
Error: 1.53 ppm



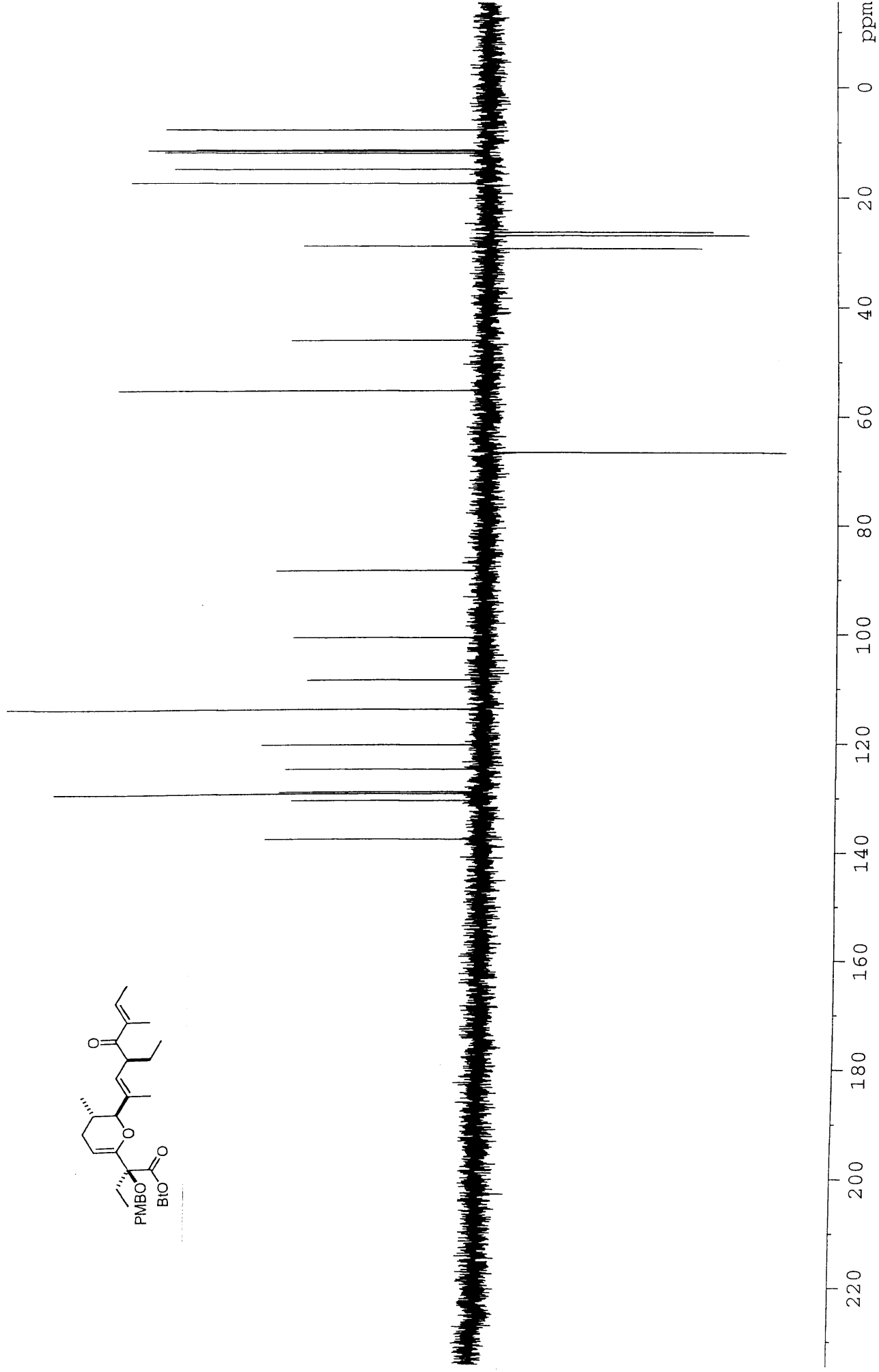
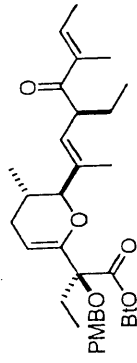
IV-JG-106  
PROTON  
CDCl<sub>3</sub>



IV-JG-106  
CARBON  
CDCl3



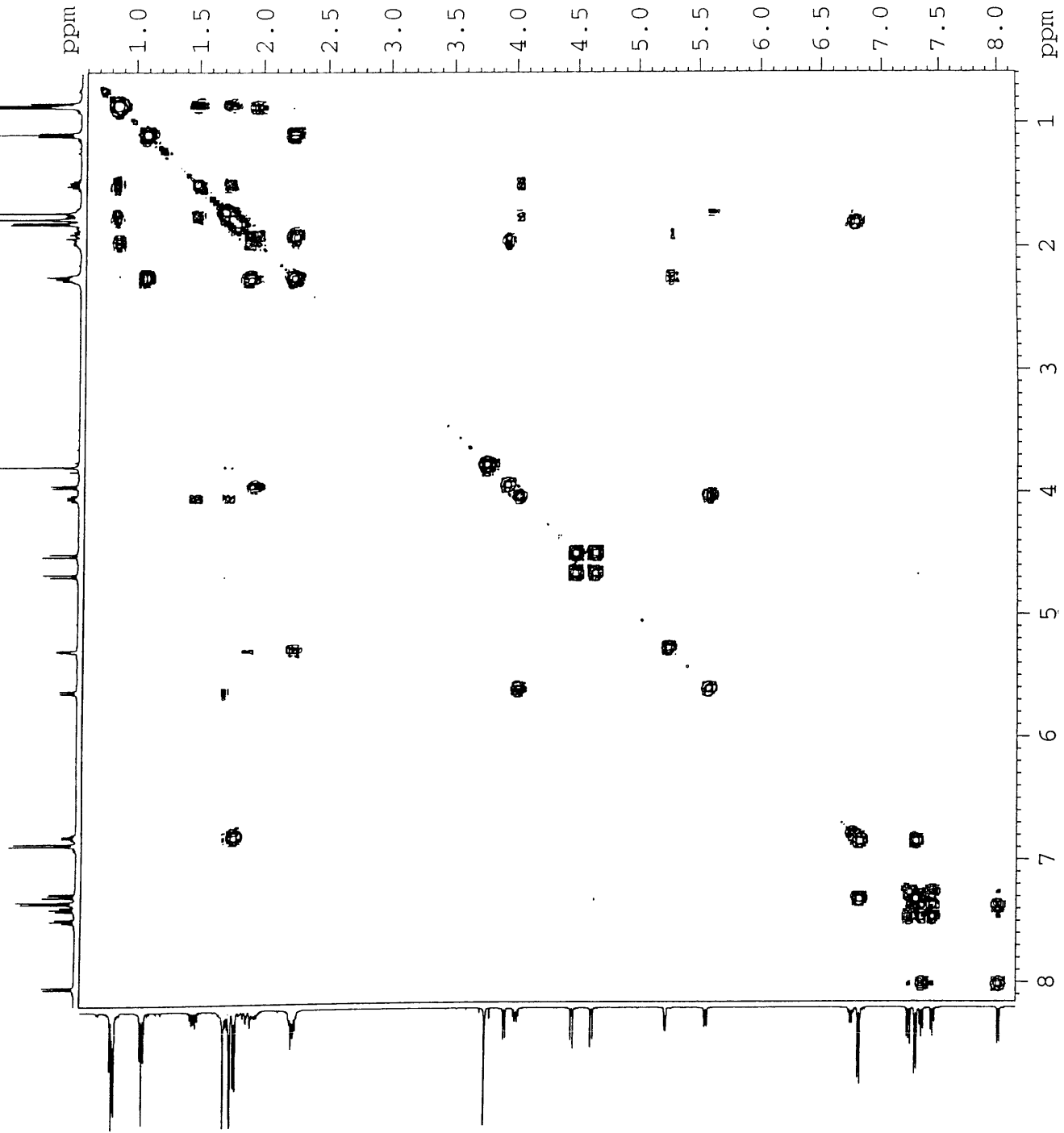
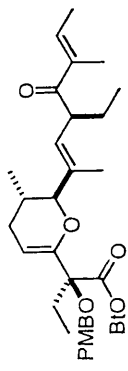
IV-JG-106  
DEPT  
CDCl<sub>3</sub>



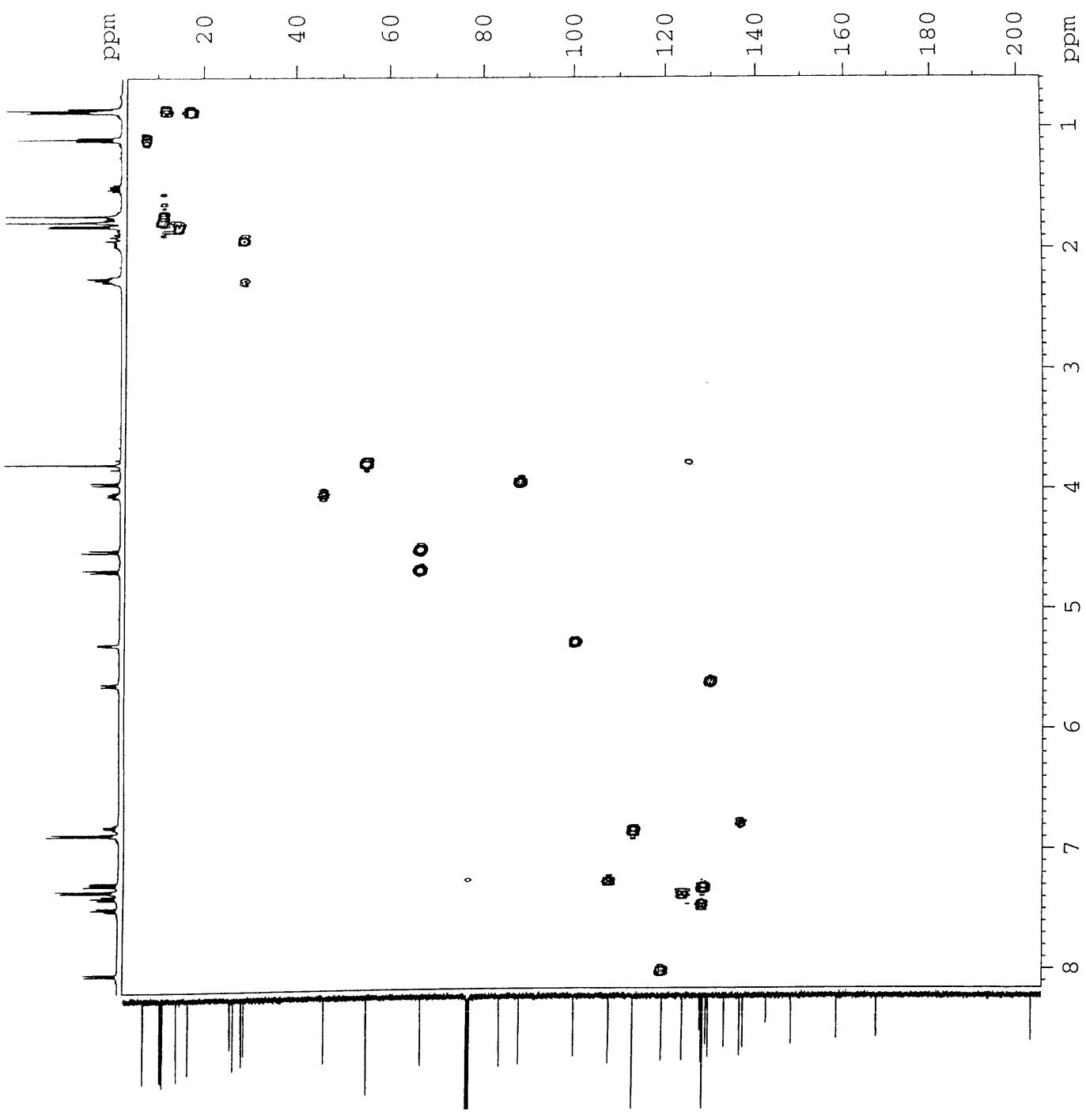
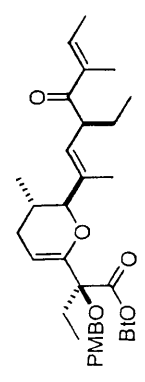
IV-JG-106

COSY

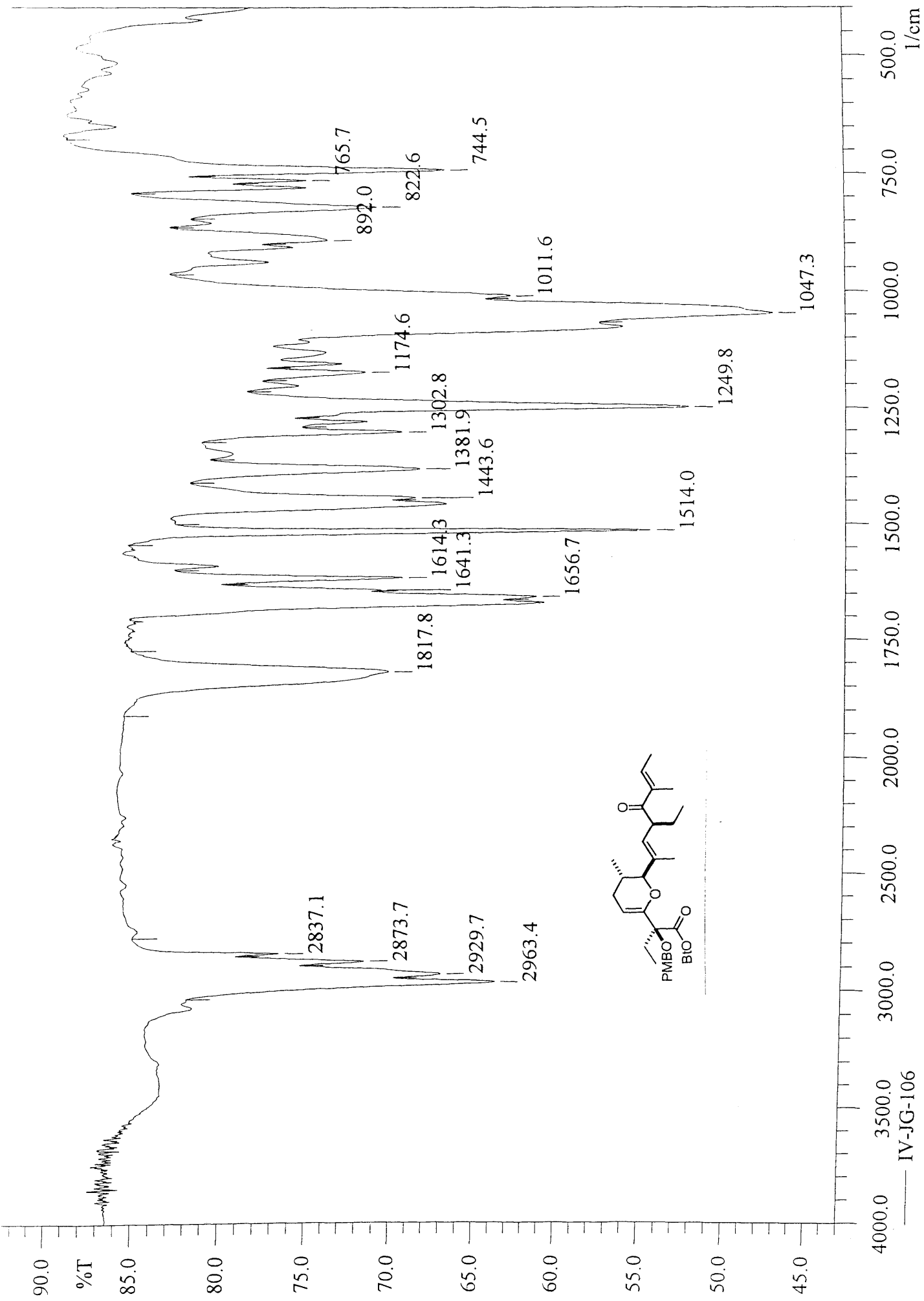
CDC13



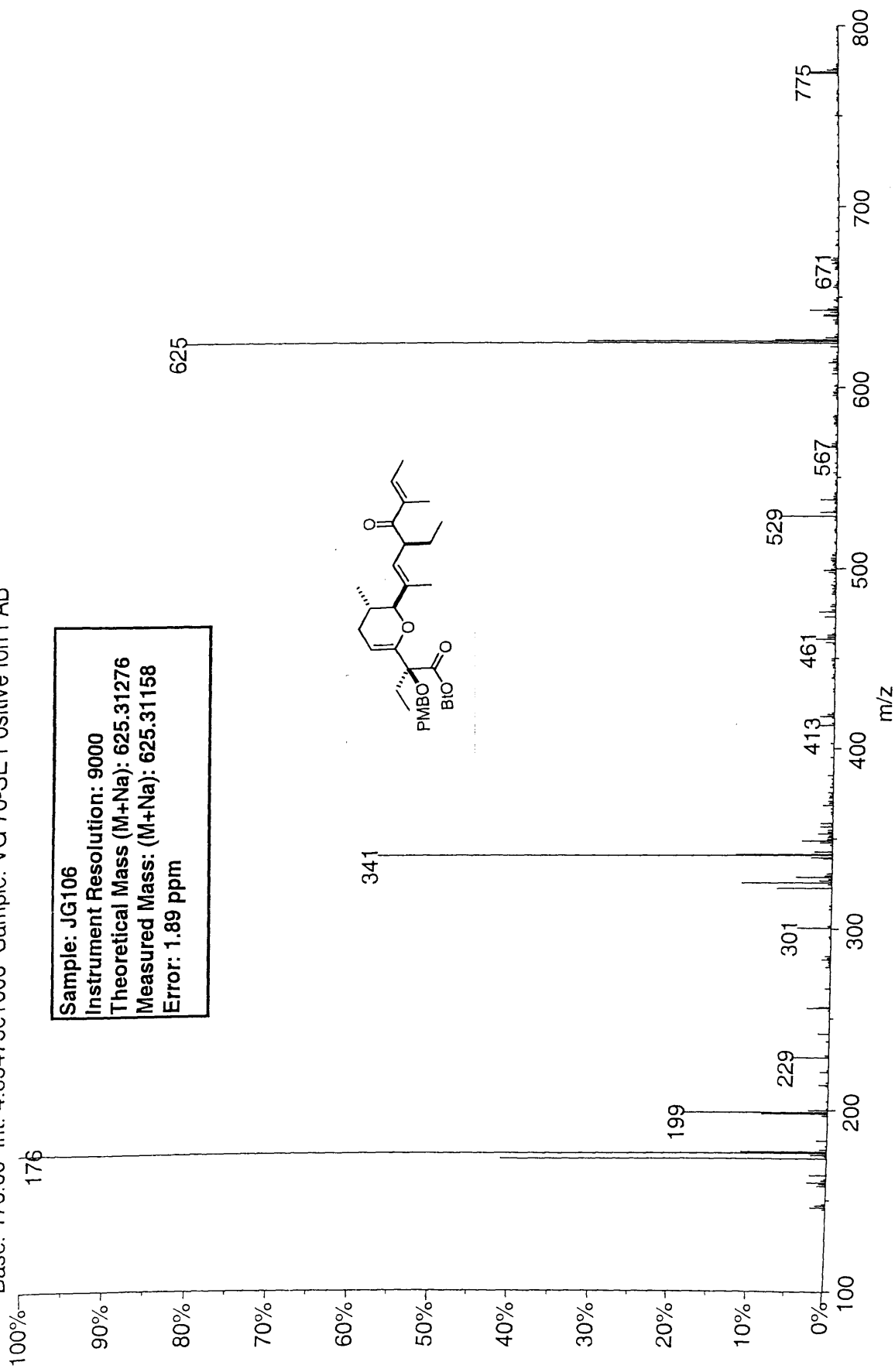
IV-JG-106  
HMQC  
CDC13







03080306: Scan 170 (31.12 min) - Back  
Base: 176.00 Int: 4.35475e+006 Sample: VG 70-SE Positive Ion FAB



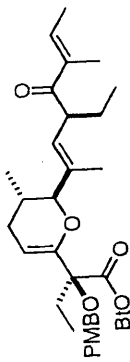
Sample: JG106

Instrument Resolution: 9000

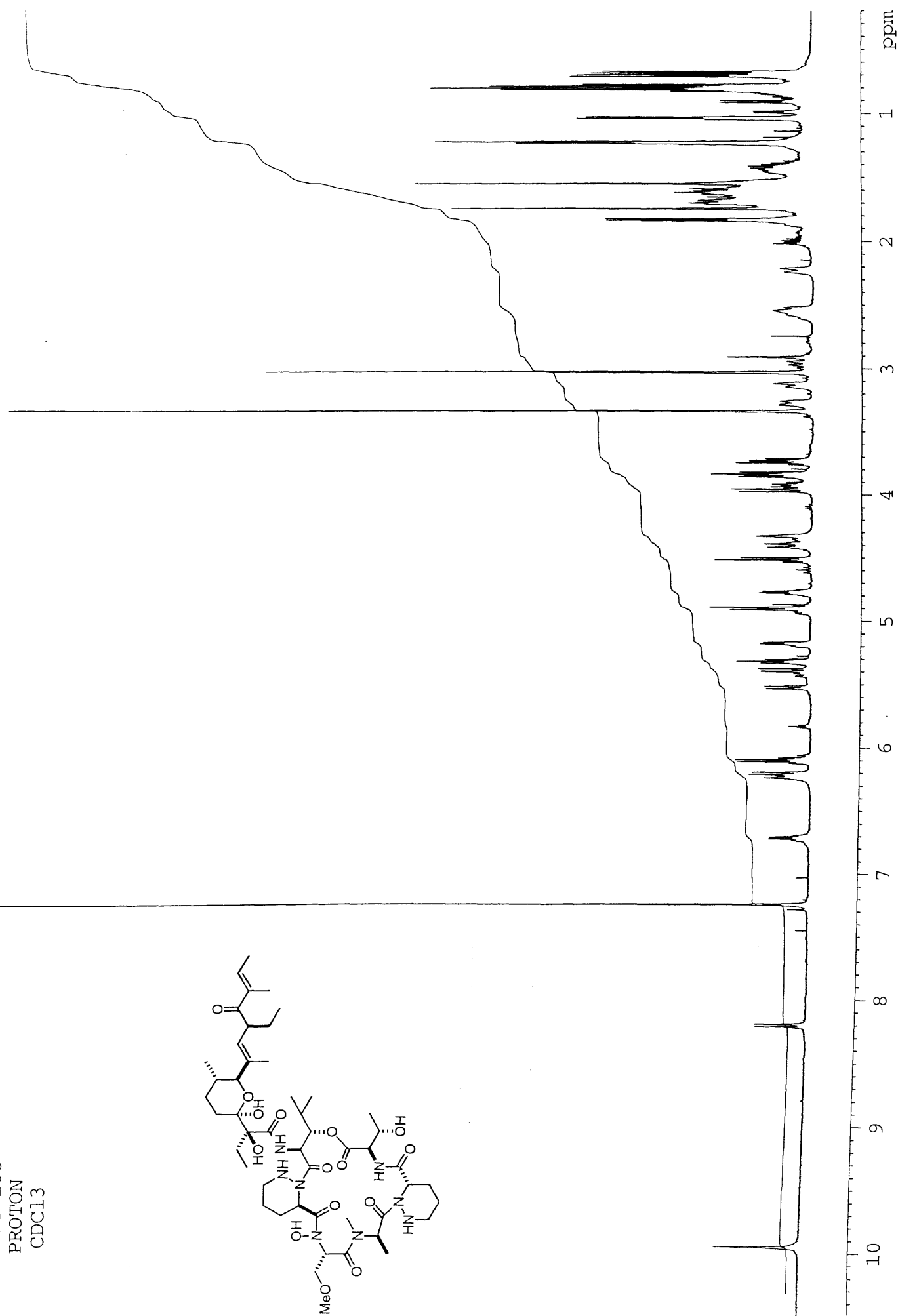
Theoretical Mass (M+Na): 625.31276

Measured Mass: (M+Na): 625.31158

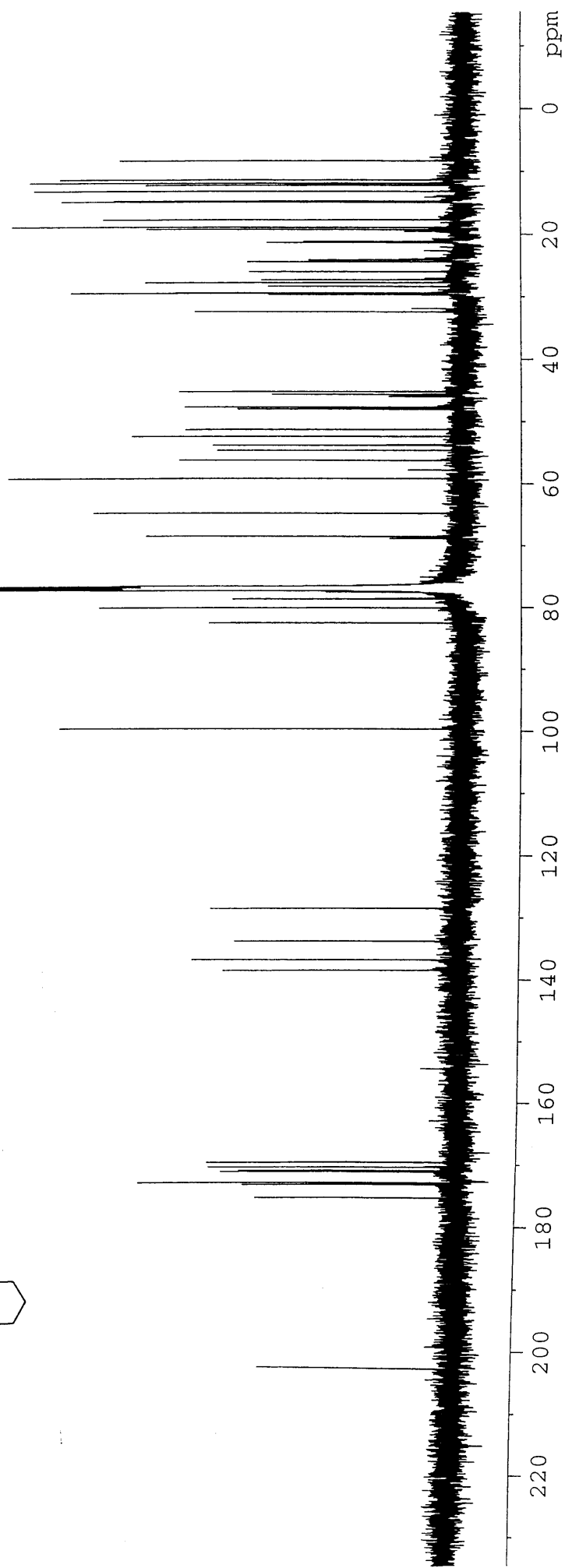
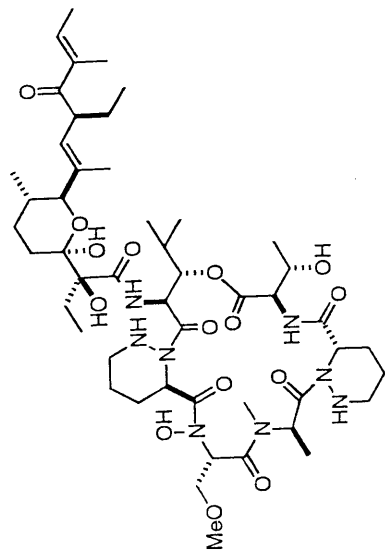
Error: 1.89 ppm



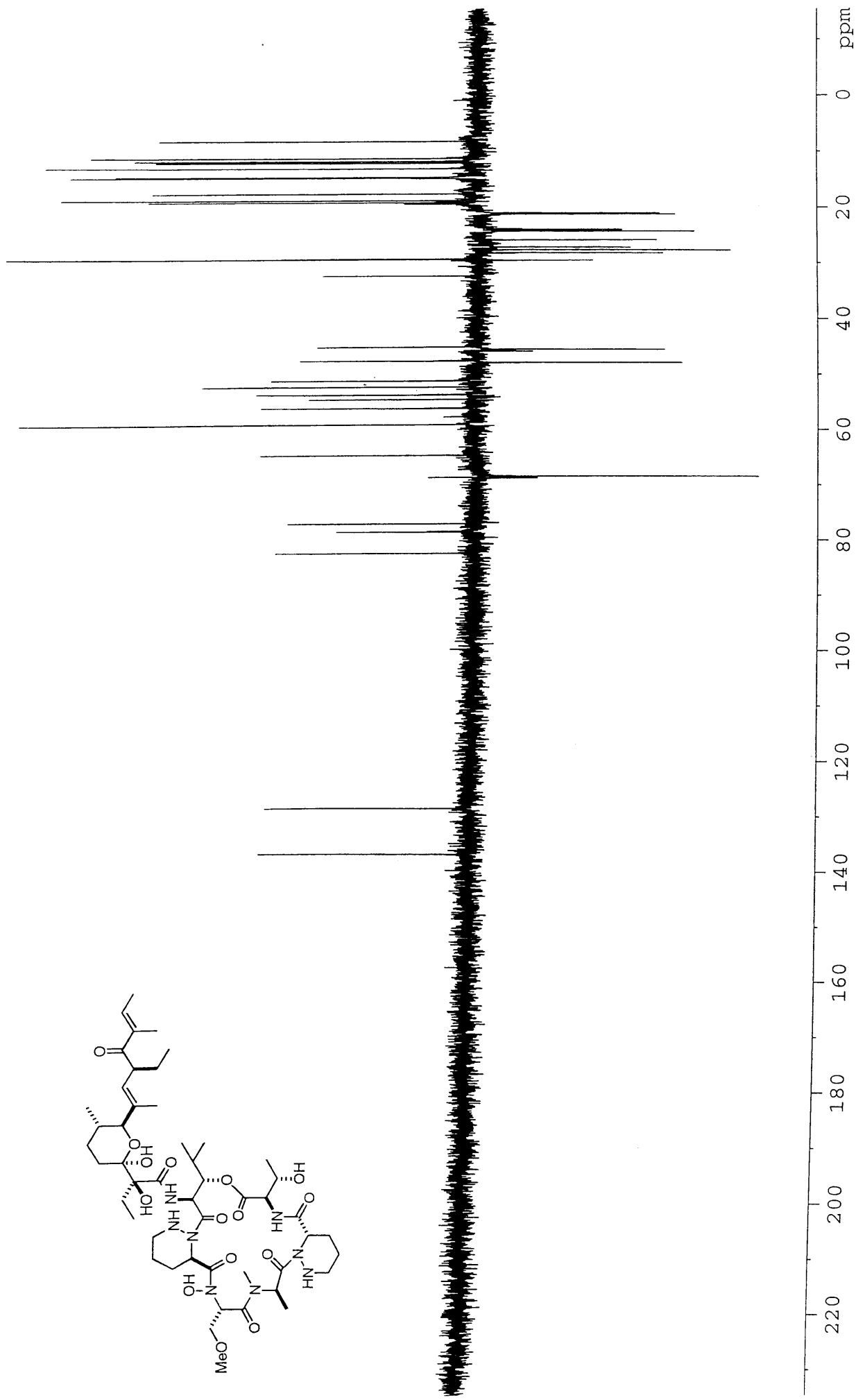
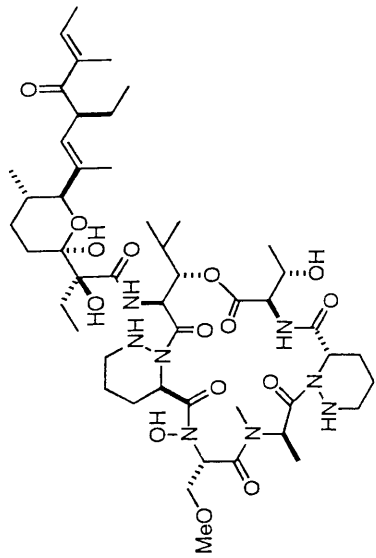
CDC13



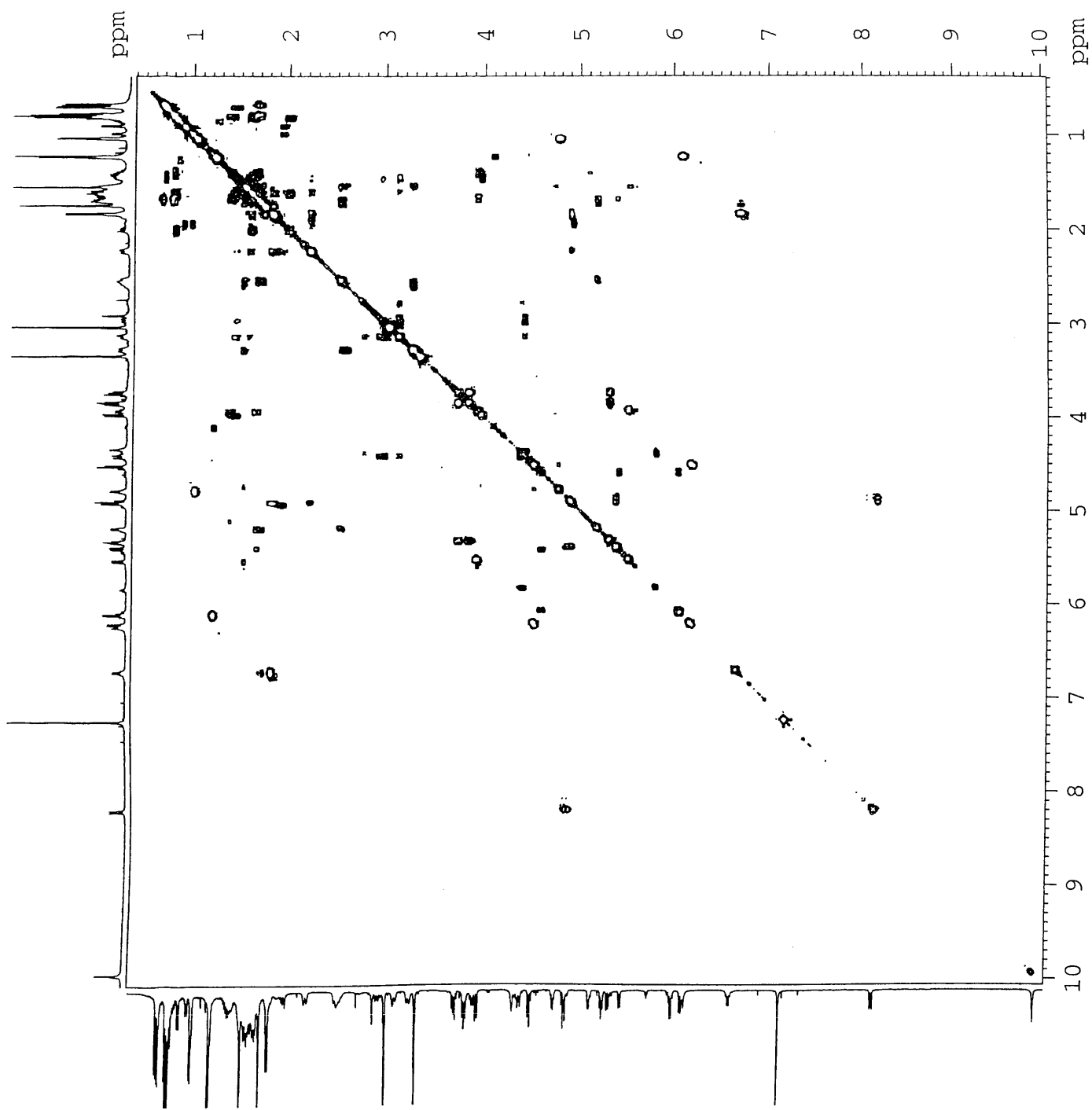
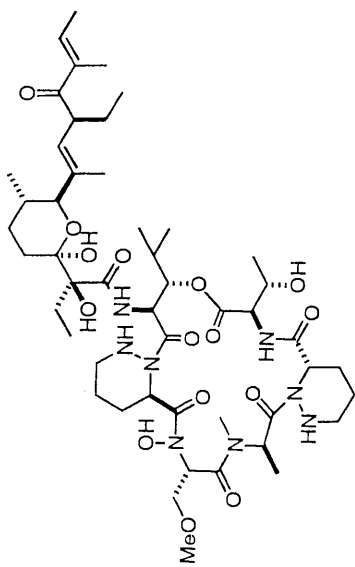
IV-JG-108  
CARBON  
CDC13



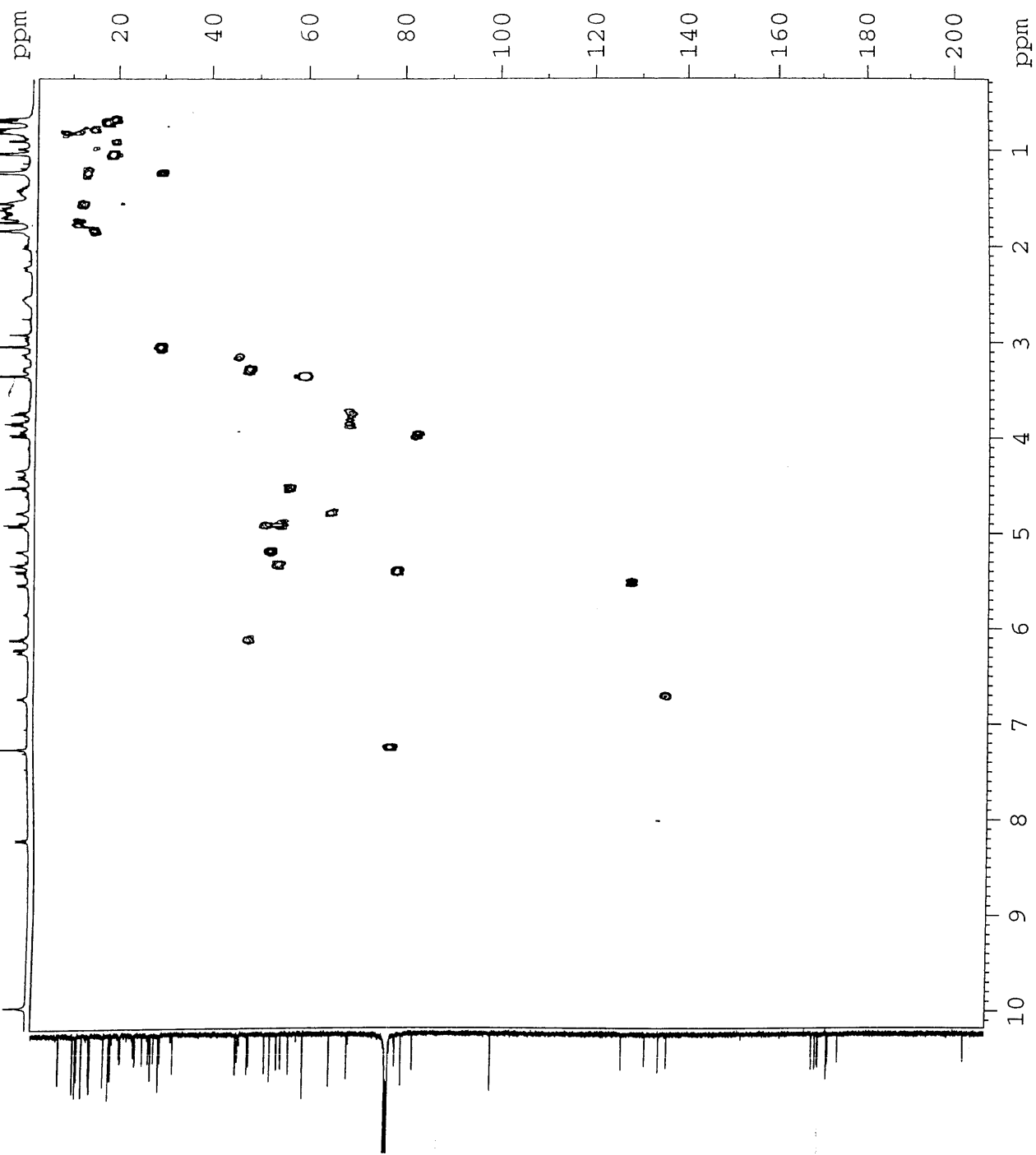
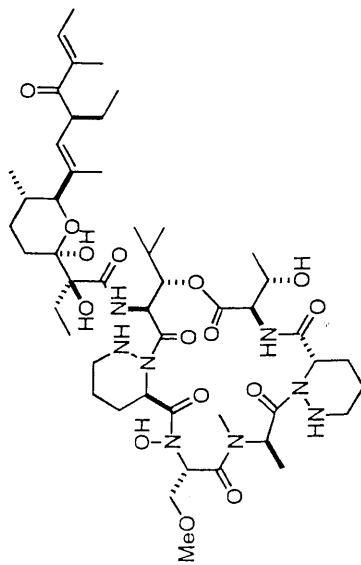
IV-JG-108  
DEPT  
CDCl<sub>3</sub>



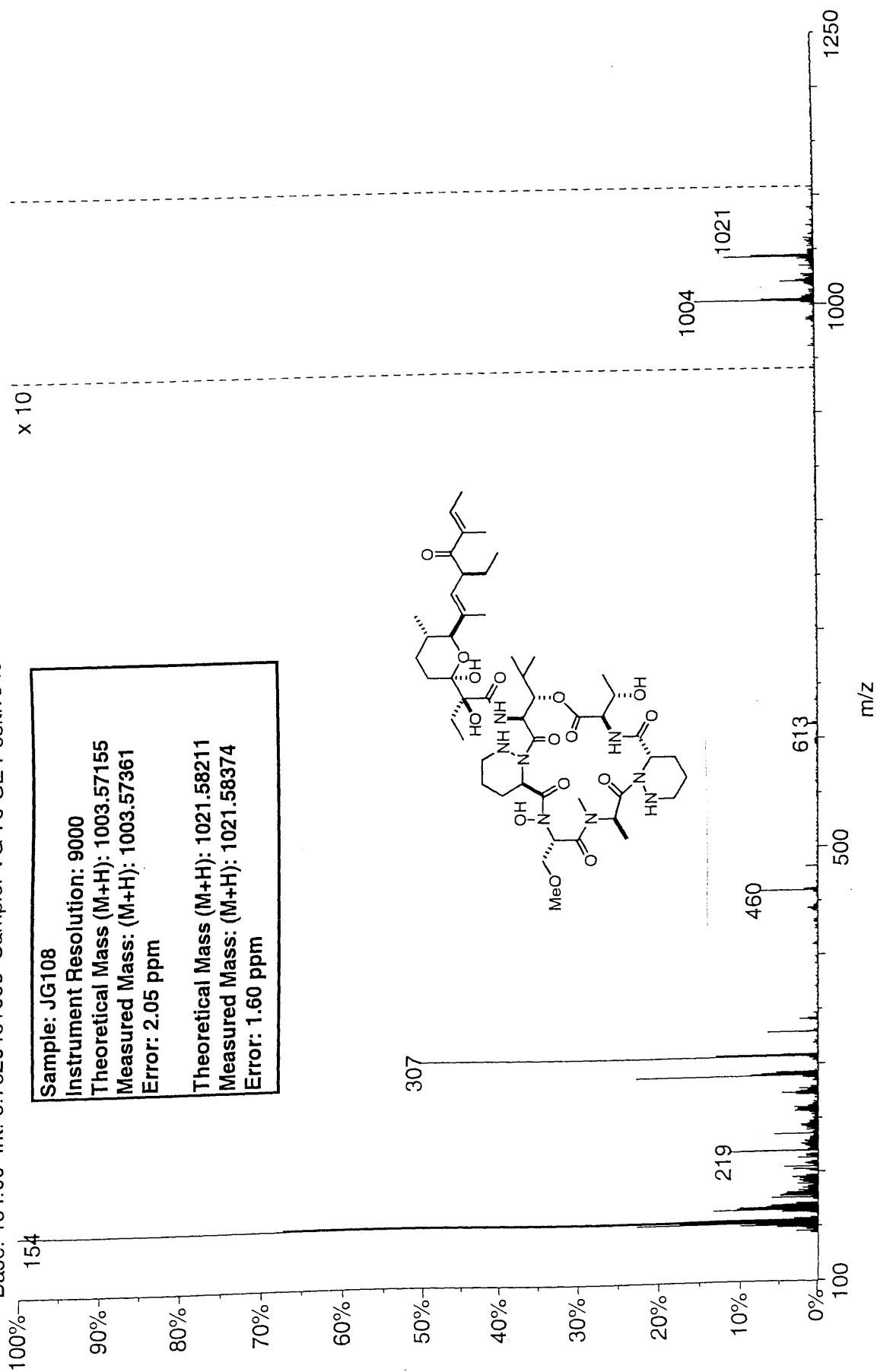
CDC13



IV-JG-108  
HMQC  
CDC13



03080306: Scan 227 (41.57 min) - Back  
Base: 154.00 Int: 5.73204e+006 Sample: VG 70-SE Positive Ion FAB

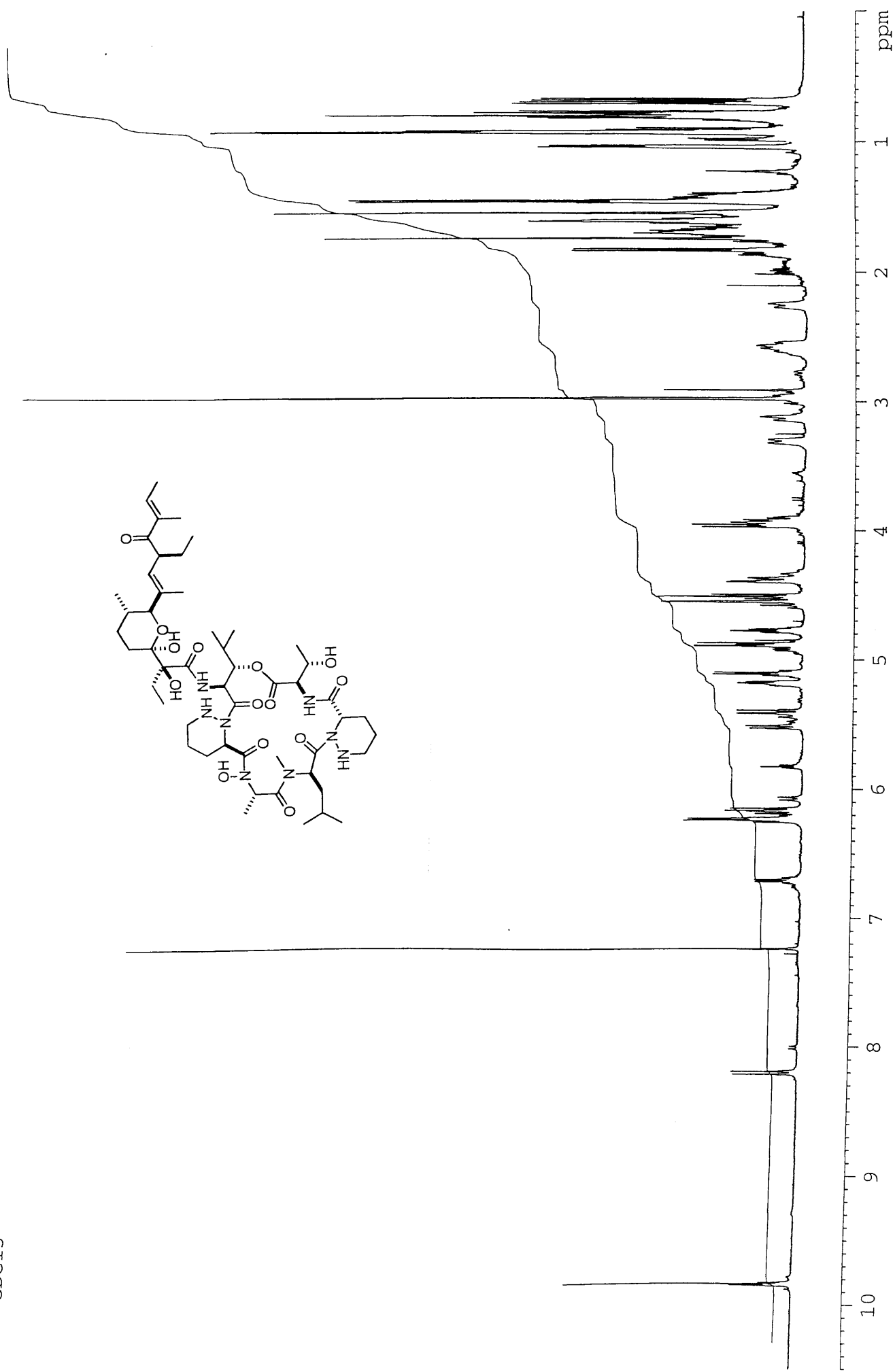




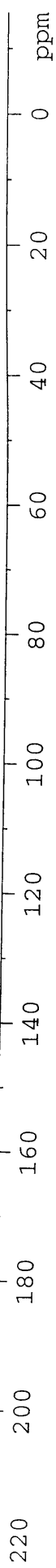
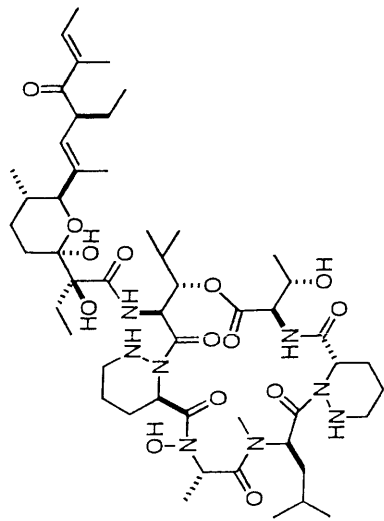
IV-JG-140

PROTON

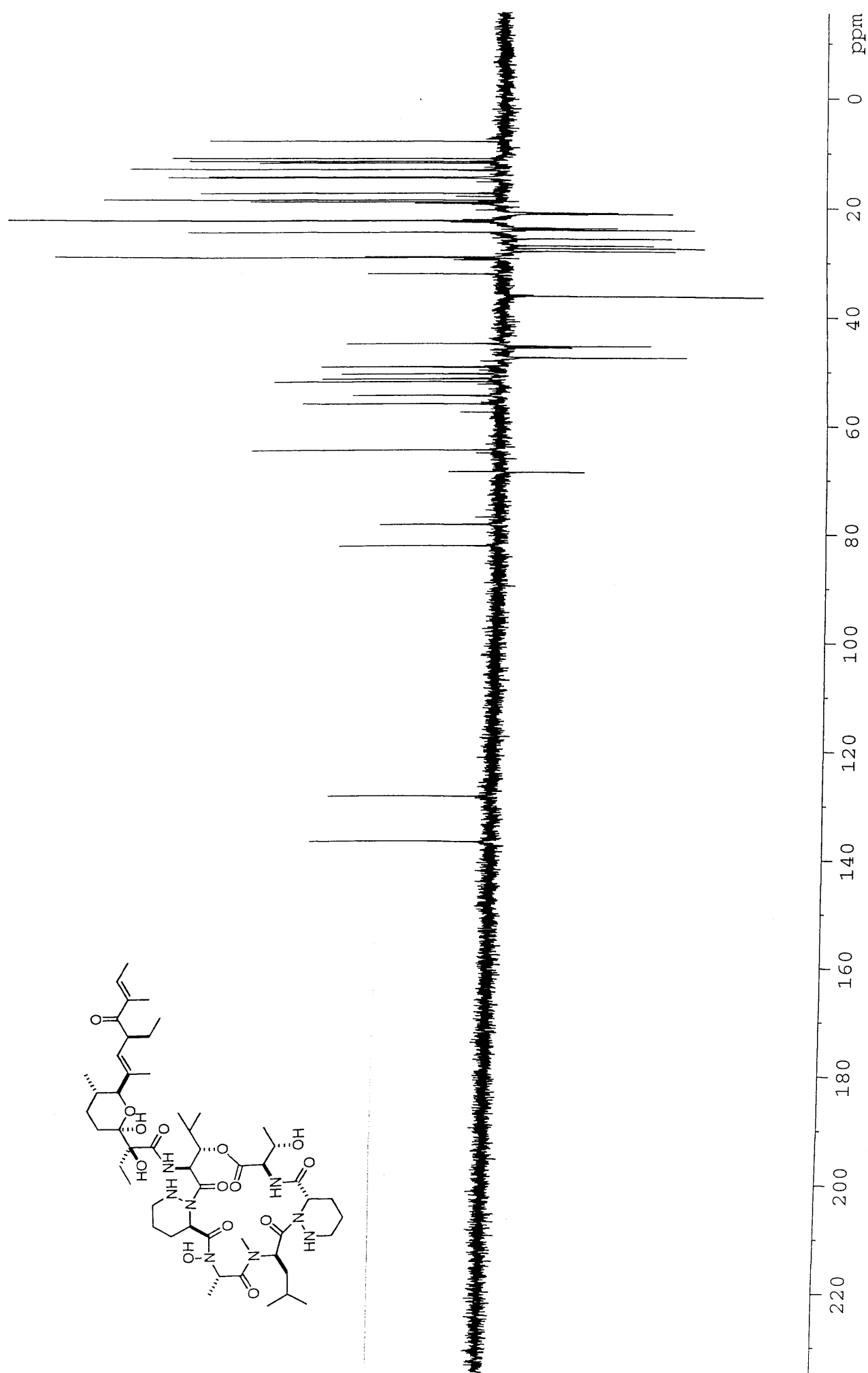
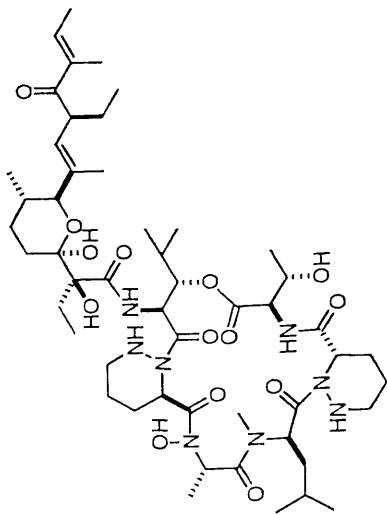
CDC13



IV-JG-140  
CARBON  
CDCl<sub>3</sub>



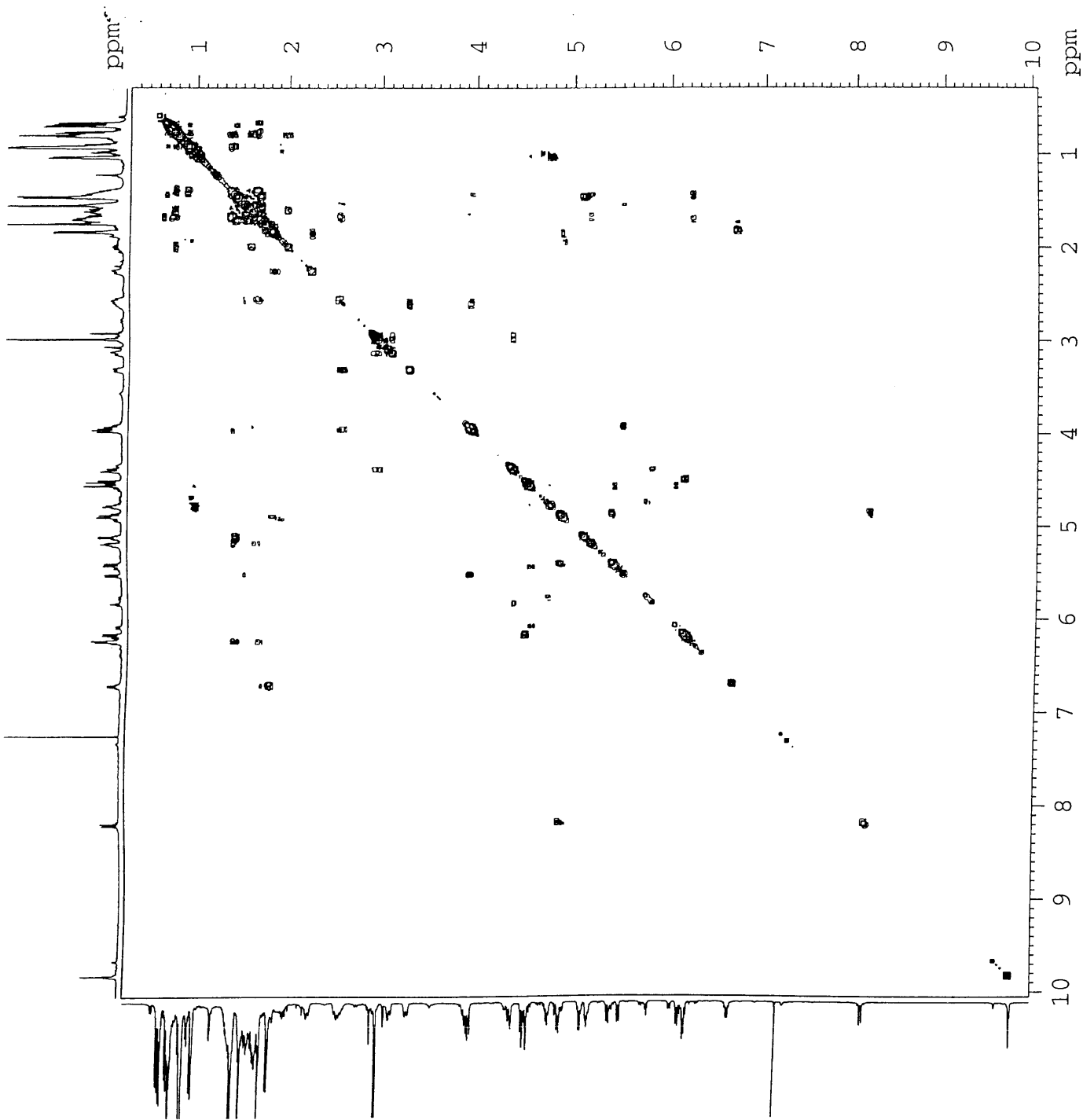
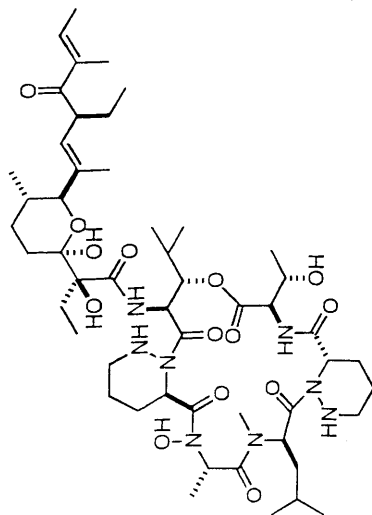
IV-JG-140  
DEPT  
CDCl<sub>3</sub>



IV-JG-140

COSY

CDC13



IV-JG-140  
HMQC  
CDC13

